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(54) **Novel imidazo(1,2-a)pyridines and pyrazines, processes for their preparation and pharmaceutical compositions containing them.**

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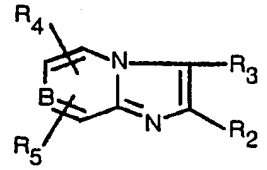
Description

This invention relates to novel imidazo[1,2-a]pyridines and pyrazines, to process for their preparation, to pharmaceutical compositions containing such compounds and to methods for preparing such compositions. The compounds are particularly useful for treating peptic ulcer disease.

Certain substituted imidazo[1,2-a]pyridines and their use as anthelmintic agents are known, e.g. from USP 4,177,274. They differ in structure from the compounds of this invention, and their published use does not suggest any use of structurally related compounds in the treatment of peptic ulcer.

Compounds closely related to, though different in structure from those of this invention, and their use for the treatment of peptic ulcer, have been described in EP—A1—0033094, published after the priority date of this invention.

The imidazo[1,2-a]pyridines and pyrazines of this invention include compounds of the general formula



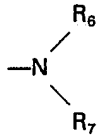
I

wherein B is CH or N; whereby, when B represents CH, then

R_2 represents hydrogen, C_1—C_6alkyl or hydroxy C_1—C_6alkyl;

R_5 represents hydrogen, halogen, or C_1—C_6alkyl; and either

R_3 is C_1—C_6alkyl, —CH_2CN, hydroxyC_1—C_6alkyl, —NO, —CH_2NC or

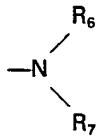


or, provided R_2 is not hydrogen, also hydrogen and

R_4 being attached to any of positions 5, 6 or 7 of the nucleus, represents any of the groupings —O—R_8—Ar, —NH—R_8—AR, —R_8—Ar, —CH=CH—Ar, —CH=CH—CH_2—Ar or —O—CH_2—CH=CH_2; or

R_3 is as defined above and

R_4 being attachd to the 8-position of the nucleus, represents any of the groupings:
—CH=CH—Ar, —CH=CH—CH_2—Ar or —O—CH_2—CH=CH_2; or
R_3 is —NO, —CH_2NC or



and

R_4, being attached to the 8-position of the nucleus, represents —O—R_8—Ar, —NH—R_8—AR, —R_8—Ar; and when B represents N, then

R_5 is as above defined,

R_2 and R_3 are independently selected from hydrogen, C_1—C_6alkyl, hydroxyC_1—C_6alkyl, —CH_2CN, —NO and —NR_6R_7 and

R_4 is —O—R_8—Ar, —NH—R_8—AR, —R_8—Ar, —CH=CH—Ar or —CH=CH—CH_2—Ar whereby in the above definitions, R_6 and R_7 are independently selected from hydrogen or C_1—C_6alkyl;

R_8 is a straight- or branched- chainC_1—C_6alkylene group; and

Ar represents thienyl, furanyl, pyridyl, phenyl or phenyl substituted by one or more substituents selected from halogen and C_1—C_6alkyl;

the 2,3-dihydro; 5,6,7,8-tetrahydro and 2,3,5,6,7,8-hexahydro derivatives thereof and the pharmaceutically acceptable salts of such compounds.

As used herein, the term "halogen" includes fluoro, chloro, bromo and iodo, with fluoro and chloro being preferred; the term "C_1—C_6alkyl" means straight and branched chain hydrocarbon groups having up to six carbon atoms such as methyl, ethyl, propyl, butyl, t-butyl, isopropyl, neopentyl, dimethylbutyl etc, whereby methyl and ethyl are preferred. Equally the lower alkylene gorups represented by R_8 are such having 1 to 6 carbon atoms with ethylene, methylene and propylene being preferred.

The term "pyridyl" includes the 2-, 3- and 4-isomers and the terms "thienyl" and "furanyl" include the 2- and 3-isomers.

In those instances where R_5 is other than hydrogen, such substituent may be at any of the positions 5-, 6-, 7- or 8- of the imidazo[1,2-a]pyridine nucleus or that any of positions 5-, 6- or 8- of the imidazo[1,2-

a]pyrazine nucleus which is not occupied by the group R_4. The preferred position of the R_4-group is the 8-position in the nucleus.

I One preferred group of compounds are those wherein B is CH;

R_2 represents $-CH_3$ or C_2H_5;

R_5 is hdyrogen or $-CH_3$;

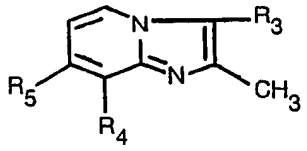
R_3 is $-NH_2$, $-NHC_2H_5$, $-CH_2CN$ or $-CH_3$ and

R_4 being attached to any of positions 5, 6 or 7 is either $-O-R_8-Ar$, $-NH-R_8-AR$, $-R_8-Ar$, $-CH=CH-Ar$, or $-CH=CH-CH_2-Ar$, with R_8 being ethylene, methylene or propylene and Ar being phenyl, o-fluorophenyl, p-fluorophenyl, p-chlorophenyl, thienyl or furanyl.

II Another preferred group of compounds are those wherein B is CH, R_2, R_4 and R_5 are as defined above under I, whereby, however, R_4 is attached to the 8-position of the nucleus; and R_3 represents $-NH_2$ or $-NHC_2H_5$.

III A further group of interest consists of compounds wherein B is CH and, R_2 and R_5 are as defined above under group I; R_3 is $-CH_2CN$ or $-CH_3$ and R_4, being attached to the 8-position of the nucleus, is $-CH=CH-Ar$ or $-CH=CH-CH_2-Ar$, with Ar being as defined under I above.

IV A most preferred group of compounds consists of such having the general formula



IA

wherein R_5 is hydrogen or methyl and either

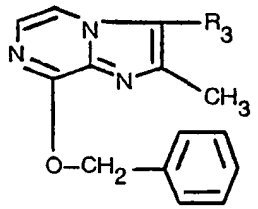
R_3 is $-NH_2$ and

R_4 is $-CH_2-CH_2-Ar$ or $-CH_2-CH_2-CH_2-Ar$; or

R_3 is $-NH_2$, $-CH_2CN$ or $-CH_3$ and

R_4 is $-CH=CH-Ar$ or $-CH=CH-CH_2-Ar$ whereby Ar represents phenyl or 3-thienyl

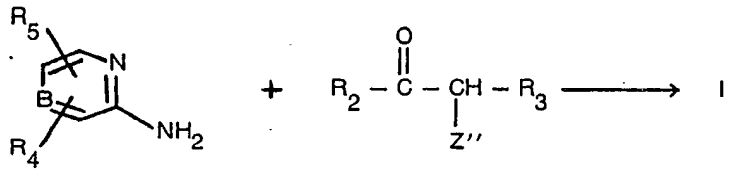
V Another most preferred group consists of compounds of formula



wherein R_3 is loweralkyl, $-CH_2CN$, $-NH_2$ or $-NHC_2H_5$.

The compounds of this invention may be obtained by processes generally known for the preparation of compounds having a similar structure. The basic step consists in formation of the (substituted) imidazo[1,2-a]pyridine- or pyrazine-nucleus. Thus, the basic process comprises the following reactions:

A:



II III

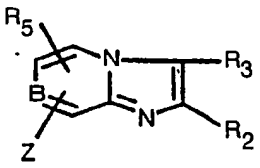
In the above formulae II and III, R_2, R_3, R_4 and R_5 are as defined hereinabove, and Z'' represents a good leaving group, preferably a reactive inorganic or organic ester group, such as halogen, tosyl, mesyl etc. Any free amino- or hydroxy groups present in R_2 and R_3, may advantageously be protected by a protecting group, which is subsequently removed. The reaction is preferably carried out by heating the reactants together (e.g. at reflux temperature) in an inert solvent.

If in the above reaction a compound of Formula III wherein R_2 and R_3 are both hydrogen and Z'' is chlorine is used (chloracetaldehyde), then R_2 and R_3 in the final compound are both hydrogen.

These compounds are intermediates useful in the preparation of compounds falling within the scope of this invention, e.g. as used in Step (ii) of process E hereinbelow:

If a compound of Formula III wherein R_2 is methyl, R_3 is hydrogen and Z'' is chlorine (chloroacetone) is used, then a compound wherein R_2 is methyl and R_3 is hydrogen or obtained.

For preparing compounds wherein R_4 represents —O—R_8—Ar, —O—$CH_2CH{=}CH_2$, —NH—R_8—Ar, or —R_8—Ar, the following process may be used

B:  + Hal – Z' ⟶ I

IV V

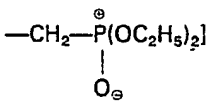
In the above formula IV and V Hal represents Br, Cl or J; Z represents halogen (Cl, Br, J), OH or NH_2, R_2, R_3 and R_5 are as above defined and Z' represents either —R_8—Ar or —CH_2—CH=CH_2 with R_8 and Ar being as defined above.

The reactants are heated together under standard reaction conditions known from the preparation of similar compounds, e.g. in an inert solvent in the presence of a base. When Z represents halogen, a copper catalyst is preferably used. When Z represents OH, or NH_2 the reaction may be carried out with or without such copper catalyst.

The starting compound of Formula IV may be obtained according to process A above, i.e. by reacting a compound of Formula II (wherein R_4 is replaced by Z) with a compound of Formula III.

C: Compounds of Formula I wherein R_4 represents —CH=CH—Ar or —CH=CH—CH_2—Ar are preferably prepared from a compound of Formula IV wherein Z represents a CHO— group through a Wittig reaction or a modification thereof. Again the starting compounds of Formula IV needed for this process may be prepared according to process A above. The Wittig reagents to be used are preferably well-known dialkylphosphonates. Thus by using a diethylbenzylphosphonate in the above reaction a compound wherein R_4 is phenylethenyl is obtained.

D: Alternatively the compounds of this invention wherein R_4 represents —CH=CH—Ar may be obtained by reacting a compound of Formula IV wherein Z represents a phosphinylmethyl group [e.g.



with a compound Ar—CHO. The starting phosphonate of Formula IV may be prepared as exemplified below:

A compound of Formula IV wherein Z represents —CHO (prepared by using process A above) is reduced (e.g. with $NaBH_4$) to the corresponding hydroxymethyl compound.

Chlorination thereof, e.g. with $SOCl_2$, replaces the OH group by Cl and reaction of the resulting compound wherein Z is —CH_2Cl with $P(OC_2H_5)_3$ provides the desired starting compound.

For preparing compounds of Formula I wherein R_3 represents the group CH_2CN, the following process may be applied:

E: A compound of general Formula I wherein R_2, R_4 and R_5 are as defined for Formula I but wherein R_3 is replaced by a group CH_2X (wherein X represents a good leaving group), is reacted with a metal cyanide to yield the desired product. Preferred leaving groups are halogen, alkoxy, aryloxy, mesyl, tosyl, quaternary groups such as $\overset{\oplus}{N}(CH_3)_3.J^{\ominus}$ and quaternary groups wherein the quaternary ion is a non-nucleophilic counter ion such as $BF_4^{\ominus}$, $PF_6^{\ominus}$, $CF_3SO_3^{\ominus}$, $FSO_3^{\ominus}$, etc. Additionally one may carry out the displacement reaction in the presence of a crown ether. The preferred metal cyanides are alkali metal cyanides.

The reaction is carried out under standard conditions, e.g. by heating the reactants in an inert solvent, preferably dimethylformamide. When the quaternary anion is a non-nucleophilic counter ion, the reaction may also be carried out in an aqueous solvent.

The starting compounds of this process may be obtained by standard procedures, e.g. as illustrated below for the quaternary iodide salt:

(i) A compound of Formula II is reacted with a compound of Formula III whereni R_3 is hydrogen according to process A above.

(ii) The compound resulting from step (i), which is a compound of Formula I wherein R_3 is hdyrogen, is further reacted with dimethylamine hydrochloride and paraformaldehyde by heating the reactants in methanol at reflux temperature.

(iii) The compound of step (ii) is a compound of Formula I wherein R_3 represents —$CH_2N(CH_3)_2$ is reacted with CH_3J to yield the desired methiodide.

Starting compounds wherein X represents halogen may be obtained from the corresponding compound wherein X is hydroxy through chlorination, e.g. by treatment with phosphorylchloride.

F: Compounds wherein R_2 and/or R_3 represent an hydroxy-loweralkyl group may be prepared by reducing a compound of Formula I wherein R_2 and/or R_3 is the group —$(R')_nCOOR$ (R' being a lower

alkylene group with 1 to 5 carbon atoms, R being a hydrocarbon group and n being zero to one).

Thus, reduction of a compound of Formula I wherein R_3 is replaced by $—COOC_2H_5$, e.g. by using lithium aluminium hydride in tetrahydrofuran, yields the corresponding compound of Formula I wherein R_3 is $—CH_2OH$.

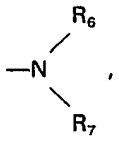
The starting compound (i.e. a compound wherein R_2 and/or R_3 is $—(R')_nCOOR$ may be prepared according to process A above by using a compound of Formula III providing the desired carboxylic acid ester group in the 2- or 3- position.

As is obvious to any one skilled in the art, numerous standard reactions may be used for introducing a specific R_2 and/or R_3 group into the molecule or for substituting one type of R_2 and/or R_3 by another.

G: Compounds wherein R_3 represents —NO may be prepared by nitrousation of a compound of Formula I wherein R_3 is hydrogen. The reaction is carried out under standard conditions, e.g. by reaction with a nitrile (soidum nitrite) in the presence of HCl.

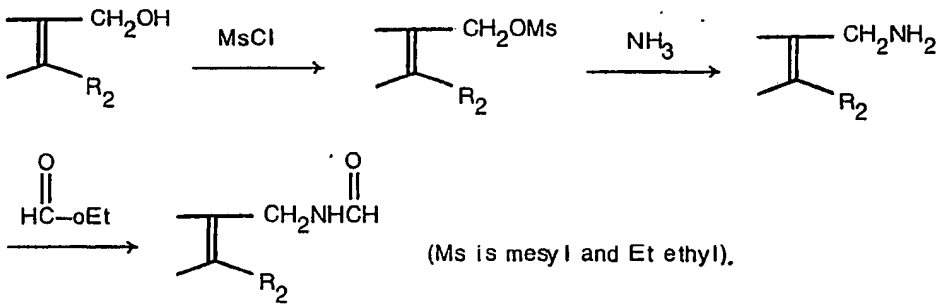
H: Compounds of Formula I obtained according to process G above may be used for the preparation of compounds wherein R_3 represents $—NH_2$ in that the nitroso compound is subjected to a standard reduction procedure, e.g. by means of zinc powder in acetic acid. Starting compounds having NO_2 instead of NO may likewise be reduced.

I: The compounds wherein R_3 represents



with R_6 and/or R_7 being loweralkyl, are preferably prepared by simple alkylation of compounds of Formula I wherein R_3 is an amino group.

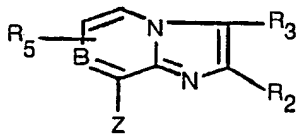
J: Compounds of Formula I wherein R_3 represents a isocyanomethyl may be prepared by reacting a compound of Formula I wherein R_3 is CH_2NHCH (O) with $POCl_3$ in the presence of an amine. The starting compound may be obtained by subjecting a compound wherein R_3 is $—CH_2OH$ to the following sequence of reaction steps:



(Ms is mesyl and Et ethyl).

The 2,3-dihydro, 5,6,7,8-tetrahydro and 2,3,5,6,7,8-hexahydro derivatives may be prepared by standard reduction procedures, e.g. by means of H_2 in the presence of a palladium catalyst.

It is also obvious to anyone skilled in the art that the sequence of certain reactions may be altered. Thus, for example, one may, in accordance with process (A) above first prepare a compound of the formula



make the above described rearrangements within the groups R_2 and R_3 and then complete the molecule by carrying out process (B) above.

Example 1

8-Benzyloxy-2-methyl-3-nitroso imidazo[1,2-a]pyridine

Step A: Preparation of 2-amino-3-benzyloxypyridine.

In a 12 liter 3-neck round bottom flask equipped with mechanical stirrer and thermometer there were placed 2.5 liters of 40% sodium hydroxide solution, 26.5 g of Adogen 464 (Rg. Trademark) and 2.5 liters of dichloromethane. To this vigorously stirred mixture was added 550 g of 2-amino-3-hydroxypyridine. The temperature was 38°C. The brown orange mixture was cooled to 25°C, and 677.5 g of benzylchloride was added in one portion and the mixture was allowed to separate into 2 phases. The lower aqueous phase was

separated and diluted with 1 liter of ice:water. This solution was then extracted with dichloromethane (3 × 15 liters). The combined dichloromethane extracts were added to the original dichloromethane phase, washed with 1 liter of saturated sodium chloride solution and dried over potassium carbonate. The dichloromethane extract was filtered and concentrated on the rotary evaporator to an orange solid. This solid was dissolved in 1 liter of boiling absolute ethanol, and the solution was filtered. The filtrate was chilled, and the crystals that formed were filtered, washed with 500 ml of ethanol at −10°C, and dried at 50°C. in a vacuum oven, to give the desired product.

Step B: Preparation of 8-benzyloxy-2-methyl-imidazo[1,2-a]pyridine

Into a 12 liter 3-necked flask equipped with a mechanical stirrer and condenser, were placed 750 g of 2-amino-3-benzyloxy-pyridine (obtained according to Step A), 6.75 liters of absolute ethanol (one may also use methanol 3 liters) and 360 ml of chloroacetone. The solution was heated under reflux for 4 hours.

An additional 180 ml of chloroacetone was added and the dark solution was heated under reflux for 18 hours. The solvent was evaporated off and the residual dark oil was dissolved in 7 liters of water. The resulting solution was made strongly basic with 15% sodium hydroxide and the basified solution was extracted with several portions (4 × 1.5 liters) of dichloromethane. The extracts were combined and washed with brine and the washed extracts evaporated down to a dark gum which was boiled with 7 liters of diisopropyl ether. The solution was decanted from insoluble material through a glass wool plug, and the filtrate was chilled. The resulting crystals were filtered and washed with cold diisopropyl ether.

Recrystallization provided the pure product of this example (m.p. 93—95°C.)

Step C: Preparation of title compound

To a stirred mixture of 10.0 g (42.2 mmol) of 8-benzyloxy-2-methyl-imidazo[1,2-a]pyridine, 150 ml of water and 150 ml of chloroform is added cautiously (EXOTHERM) 179.5 ml (2.15 moles) of concentrated hydrochloric acid and the resultant mixture is heated to an internal temperature of approximately 55°C. To this stirred and heated mixture is added at a rate of approximately 7 ml/minute a solution of 151 g (2.11 moles) sodium nitrate (97%) in 600 ml of water to produce a vigorous, but manageable, reflux. When the addition is complete, the reaction mixture is allowed to cool to room temperature. The lower ($CHCl_3$) layer is drawn off and the aqueous layer extracted with three — 150 ml portions of chloroform. The combined chloroform extracts are washed with two — 450 ml volumes of 2.4 *M* sodium carbonate solution, then with a single 500 ml portion of saturated aqueous sodium chloride. The extracts are concentrated *in vacuo* (rotary evaporator, 45°C.) to less than one-half the original volume, dried over anhydrous sodium sulfate and evaporated to a viscous oil. Chromatography of the oil on silica gel, eluting with chloroform/ethyl acetate (1/1) yields the title compound as a given crystalline solid, mp 147.5—149.5°C. (dec).

Example II

3-Amino-8-benzyloxy-2-methyl-imidazo[1,2-a]pyridine phosphate

A.

To a stirred mixture of 3.2 g (12 mmol) of 8-benzyloxy-2-methyl-3-nitroso-imidazo[1,2-a]pyridine in 24 ml of glacial acetic acid and 33.5 ml of water is added portionwise 3.23 g (49.5 mmol) of zinc powder over a two hour period. When addition is complete, the reaction mixture is stirred at room temperature for 30 minutes. The mixture is filtered through Celite, and the filtrate diluted with 75 ml each of ether and methylene chloride and washed with a solution of 250 ml of 1.7 *M* sodium hydroxide. The resultant emulsion is filtered through Celite and the Celite pad washed thoroughly with 250 ml of hot chloroform.

The layers of the filtrate are separated and the aqueous phase extracted with the chloroform used to wash the Celite pad. The combined organic extracts are washed with two-125 ml portions of water and one-150 ml volume of saturated aqueous sodium chloride and then concentrated under reduced pressure to a volume of approximately 100 ml. The concentrate is dried over anhydrous sodium sulfate and the solvent removed under reduced pressure (rotary evaporator, 40°C.) to give a slightly tacky brown powder that is triturated in ether (75 ml) — methylene chloride (1 ml) to yield the free base of the title compound as a light brown powder, mp 126—131.5°C. (dec).

B.

850 mg (3.37 mmol) of the free base is dissolved in approximately 40 ml of dry acetonitrile. To the stirred solution is added 8 ml of an acetronitrile solution containing 3.4 mmol of phosphoric acid. A precipitiate forms and the mixture is diluted with 70 ml of ether and filtered. The solid is triturated in 60 ml of fresh ether and filtered to give the crude phosphate salt which upon recrystallization from methanol — ethyl acetate yields the title phosphate salt containing 1.3 moles of water of crystallization, mp 214—214.5°C. (dec.).

Example III

5-Benzyloxy-2,3-dimethylimidazo[1,2-a]pyridine

Sodium hydride (50% in oil, 4.8 g) is added to a solution of benzyl alcohol (6.48 g) in dimethylformamide (200 ml). 5-chloro-2,3-dimethylimidazo[1,2-a]pyridine hydrobromide (10.5 g) is added and the mixture is stirred at room temperature for two hours.

The solvent is removed *in vacuo* and the residue is partitioned between water (500 ml) and ether (400 ml). The ether layer is separated, dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield a yellow oil which is chromatographed on silica gel (300 g) using ether as an eluant. After an initial fore-run of a yellow oil, the product is obtained which crystallizes from 1-chloro-butane-hexane mixture.

Similarly, the use of benzylamine in place of benzyl alcohol gives 5-benzylamino-2,3-dimethyl-imidazo[1,2-a]pyridine.

Example IV

7-Benzyloxy-3-cyanomethyl-2-methylimidazo[1,2-a]pyridine

Step A: Preparation of 3-chloro-4-oxopentanonitrile.

Into a 1-neck, 3-1 round bottom flask there were placed 1 l diethylether (Et_2O) and 100 g 4-oxopentanonitrile. The magnetically stirred solution was cooled to 0—5°C., one drop HCl/Et_2O added, and 185 ml 97% of SO_2Cl_2 previously chilled to 5—10°C. was added all at once. The ice bath was removed, and the pale greenish-yellow solution was warmed to 20 ± 1°C. over 5 min. by a hot water bath. The temperature was maintained at 20 ± 1°C. by a cold water bath for 2½ hours. The pale yellow solution was evaporated on a rotary evaporator in a 30°C. water bath at 80 mm vacuum, and carefully watched. Near the end of solvent removal, the *instant* the near-colourless residue began to turn orange, the flask was removed *quickly* and diluted with 1 l cold Et_2O. One ml SO_2Cl_2 was added and stirred 15 min., and the orangish solution was diluted with 1 l cold Et_2O.

The ether solution was washed with 1 l cold was washed with 1 l cold saturated $NaHC_3$-solution which was in turn extracted with 2 × 1/2 l cold CH_2Cl_2. The CH_2Cl_2 was evaporated, the residue dissolved in 200 ml Et_2O, and added to the bicarbonate-washed ether solution. The ether was extracted by 2 × 1 l col 10% $NaHSO_3$-solution and discarded. The bisulfite solution was cooled in an ice bath and 25% NaOH was added slowly to attain pH 7 (ca. 100 ml), 100 g $NaHCO_3$ was added to saturate the solution, and it was extracted with 5 × 1 l CH_2Cl_2; 25 g K_2CO_3 was added followed by extraction with 1 l CH_2Cl, and this was repeated with another 25 g K_2CO_3 — 1 l CH_2Cl_2. The combined extracts were dried over $MgSO_4$, and evaporated to leave a brown-orange oil, estimated from pmr to contain 3-Cl isomer, 5-Cl isomer, some unknown compounds and CH_2Cl_2.

Distillation of this oil through a jacketed 15-cm Vigreux column at 0.3 mmHg gave 3-chloro-4-oxopentanonitrile (b.p. 83—93°C).

Step B: Preparation of title compound.

A solution of 2-amino-4-phenylmethoxypyridine (1.45 g) triethylamine (0.73 g) and 3-chloro-4-oxopentanonitrile (0.95 g) in methanol (40 ml) is heated under reflux for three hours. After one hour, additional 3-chloro-4-oxopentanonitrile (0.5 g) and triethylamine (0.36 g) is added. The solvent is removed *in vacuo*, and the residue is partitioned between methylene chloride (50 ml) and 2% sodium hydroxide (50 ml). The methylene chloride layer is removed and concentrated *in vacuo* to give 1.5 g of crude product

A solution of crude product (1.l g) and 0.6 ml pyridine in 20 ml p-dioxane is cooled in an ice bath and treated with 0.6 ml trifluoroacetic anhydride in 2 ml p-dioxane. After removal of the ice bath, the reaction is stirred for one hour, diluted with water (300 ml) and treated with saturated sodium bicarbonate to pH 7—8. Filtration gives 0.8 g of a solid which is chromatographed on silica gel (125 g) using 3% methanol in methylene chloride to give the product which crystallizes from ethyl acetate.

Similarly, the use of 2-amino-4-benzylaminopyridine in the above procedure yields 7-benzylamino-3-cyanomethyl-2-methyl-imidazo[1,2-a]pyridine.

Example V

8-Alloyloxy-3-cyanomethyl-2-methyl-imidazo[1,2-a]pyridine

A.

8-Benzyloxy-3-cyanomethyl-2-methyl-imidazo[1,2-a]pyridine (40 g, 0.14 mol), 1,4-cyclohexadiene (50 g, 0.62 mol), dimethylformamide (600 ml) and palladium black (2 g) are stirred together and heated. At 45°C., sudden exotherm occurs and the temperature rises rapidly to 75—80°C. Heating is discontinued and the mixture stirred for 1 hour. The catalyst is removed by filtration and the cyclohexadine removed *in vacuo*. The dimethylformamide is removed *in vacuo* (0.1 mm) at 55°C. to afford 3-cyanomethyl-2-methyl-8-hydroxy-imidazo[1,2-a]pyridine (27 g, 0.14 mol).

B.

3-3-cyanomethyl-2-methyl-8-hydroxy-imidazo[1,2-a]pyridine (60.5 g, 0.32 mol) and dry dimethylformamide (1600 ml) are stirred together and sodium hydride (15.4 g, 0.32 mol, 50% in oil) added during 15 minutes. The mixture is stirred 1.5 hours after the addition of sodium hydride. Allyl bromide (38.7 g, 0.32 mol) is added dropwise during 1 hour. After the addition of allyl bromide, the reaction is stirred for an additional 1 hour. The dimethylformamide is removed *in vacuo*. The residue partitioned between water (1 liter) and chloroform (3 liters), the organic layer separated, washed with water (1 liter) dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. Residual dimethylformamide is removed *in vacuo* (0.1 mm). The residual oil is dissolved in chloroform (300 ml) and filtered through a silica gel plug (100 g, tlc grade 60H) to remove coloured materials. This process yields 29.2 g of an oil.

C.

Treatment of the oil produced in Step B with ethereal hydrogen chloride gives 8-allyloxy-3-cyanomethyl-2-methylimidazo[1,2-a]pyridine (29.9 g, 0.11 mol.) mp 177—179°C.

Example VI

3-Cyanomethyl-2-methyl-7-(2-phenylethyl)-imidazo[1,2-a]pyridine

Step A: Preparation of 3-Dimethylaminomethyl-2-methyl-7-(2-phenylelthyl)-imidazo[1,2-a]pyridine.

Into a one-liter flask there was placed 2-methyl-7-(2-phenylethyl)-imidazo[1,2-a]pyridine (112 g) dimethylamine hydrochloride, paraformaldehyde (15.23 g) and methanol (450 ml) and the mixture was refluxed with stirring for 1.5 hours. Thereafter the mixture was boiled, open to the air, for 3/4 hours. After cooling to room temperature and treatment with concentrated hydrochloric acid (45 ml) the mixture was stirred for 18 hours, filtered and the thick white solid mass formed was washed with methanol and 200 ml of anhydrous ether and dried.

Step B: Preparation of 3-dimethylaminomethyl-2-methyl-7-(2-phenylelthyl)-imidazo[1,2-a]pyridine methiodide.

3-Dimethylaminomethyl-2-methyl-7-(2-phenylelthyl)-imidazo[1,2-a]pyridine hydrochloride (1.325 g) was dissolved in 4.5 liters of hot water. The solution was made strongly basic with 50% NaOH-solution. The chilled mixture was extracted with dichloromethane (3 × 1.5 liters) and the combined extracts were washed with brine (1.5 liters). The dichloromethane extract was concentrated on a rotary evaporator. The residual oil was dissolved in 2.5 liters of ethanol. With stirring the solution was cooled and methyl iodide (232 ml) was added dropwise over a period of 1.5 hours. The mixture was allowed to warm to room temperature overnight under continued stirring. The white precipitate was collected after about 18 hours of stirring, washed with 1.5 liters of ethanol and 3 liters of ether. The resulting product is ready for use in Step C below.

Step C: Preparation of title compound.

A mixture of the methiodide of Step A (1,552 g) and sodium cyanide (310 g) in 8.4 liters of dimethylformamide was stirred and heated in a steam bath for one hour.

The dark brown reaction mixture was poured into 30 liters of ice water and the mixture was stirred for one hour. The brown solid product was collected, washed with cold water and allowed to air dry. This material was dissolved in 3.8 liters of hot methanol and treated with hydrogen chloride gas until strongly acidic. The mixture was cooled and the product collected. After washing with methanol, acetonitrile and finally with ether the title product as the hydrochloride salt was obtained.

The salt was re-suspended in water and made strongly alkaline with 10% sodium hydroxide. The product was extracted with dichloromethane (3 × 2.5 liters) and the combined extracts concentrated on a rotary evaporator. The residue was dissolved in 3.6 liters of hot acetonitrile, and the resulting solution filtered through a glass wool plug and the filtrate was refrigerated overnight. The desired product was then washed with cold acetonitrile (mp 118°C.).

Example VII

3-Amino-2-methyl-8-(*trans*-2-phenylethenyl)-imidazo[1,2-a]pyridine hydrochloride

A. 2-Methyl-8-Formylimidazo[1,2-a]pyridine

A mixture of 2-aminonicotinaldehyde (92.8 g, 0.76 mol) and bromoacetone (114.5 g, 0.84 mol) in dimethoxyethane (980 ml) is stirred for 2 hours at room temperature and then heated at 65° with stirring for 14 hours. The solid which separates is isolated by filtration, dissolved in 800 ml absolute ethanol and heated under reflux for 6 hours. The ethanol solvent is removed under reduced pressure and the residuce treated with 138 ml 6*N* hydrochloric acid in 750 ml water for 0.5 hour. The acidic aqueous layer is washed with ether (2 × 300 ml) and basified with cooling (78 ml 50% sodium hydroxide and 25 g sodium bicarbonate). The aqueous layer is extracted with dichloromethane. The extracts are combined and dried over anhydrous sodium sulfate. Following filtration, the solvent is removed under reduced pressure to afford 2-methyl-8-formyl-imidazo[1,2-a]pyridine, mp 136—139.5°C.

B. 2-Methyl-8-hydroxymethylimidazo[1,2-a]pyridine

To a stirred suspension of 56.8 g (0.36 mol) and 2-methyl-8-formylimidazo[1,2-a]pyridine in 400 ml isopropanol at 0° is added in portions 8 g (0.21 mol) sodium borohydride. The reaction mixture is stirred at room temperature for an additional 2 hours. The excess sodium borohydride is decomposed by the addition of distilled water and the solution concentrated under reduced pressure at 50°C. The residue is dissolved in water and extracted with chloroform. The chloroform extracts are combined and dried over anhydrous sodium sulfate. Following filtration, the chloroform is removed under reduced pressure to give 2-methyl-8-hydroxymethylimidazo[1,2-a]pyridine.

C. 2-Methyl-8-chloromethylimidazo[1,2-a]pyridine

2-Methyl-8-hydroxymethylimidazo[1,2-a]pyridine 21.4 g (0.13 mol) is dissolved in 400 ml dichloromethane. To the solution at 0°C. is added dropwise with stirring 19 ml of thionyl chloride. The

reaction mixture is stirred for one hour and the dichloromethane is removed under reduced pressure. The residue is dissolved in distilled water, neutralized at 0°C. with ammonium hydroxide and extracted with dichloromethane. The extracts are combined and dried over anhydrous sodium sulfate. Following filtration, the dichloromethane is removed under reduced pressure to give 2-methyl-8-chloromethylimidazo[1,2-a]pyridine, mp. 110—112°C.

D. Diethyl (2-methyl-8-imidazo[1,2-a]pyriylmethyl) phosphonate

2-Methyl-8-chloromethylimidazo[1,2-a]pyridine 37.7 g (0.21 mol) and 91 ml triethylphosphite are heated together at 145—150°C for 2 hours. Upon cooling, the residue is triturated with petroleum ether and dissolved in ether. Insolubles are removed by filtration and the ether is evaporated under reduced pressure. The oil obtained is dissolved in dichloromethane and dried over anhydrous sodium sulfate. Following filtration, the dichloromethane is removed under reduced pressure to give diethyl (2-methyl-8-imidazo[1,2-a]pyridylmethyl) phosphonate as an oil.

E. 2-methyl-8-(2-phenylethenyl)-imidazo[1,2-a]pyridine

A solution of 48.5 g (0.17 mol) diethyl (2-methyl-8-imidazo[1,2-a]pyridylmethyl) phosphonate and 19.4 ml benzaldehyde in 400 ml dimethoxyethane is added dropwise to a stirred suspension of sodium hydride (11.6 g, 0.48 mol) in dimethoxyethane at 0°C.

After stirring overnight, the dimethoxyethane is removed under reduced pressure. The residue is dissolved in water and extracted with dichloromethane. The dichloromethane extracts are combined and dried over anhydrous sodium sulfate. Following filtration, the dichloromethane is removed under reduced pressure. Re-crystallization from ethyl acetate gives 2-methyl-8-(2-phenylethnylimidazo[1,2-a]pyridine, mp 101—105°C.

F. 3-Nitroso-2-methyl-8-(2-phenylethenyl)imidazo[1,2-a]pyridine

To a solution of 5.0 g (0.02 mol) 2-methyl-8-(2-phenylethenyl)-imidazo[1,2-a]pyridine dissolved in 40 ml acetic acid and 100 ml water at 5°C. is added in portions over 10 minutes, 2.7 g (0.04 mol) sodium nitrate. The mixture is stirred at 0°C. for 20 minutes and at room temperature for 2 hours. Additional water (50 ml) is added, the solid is isolated by filtration and washed thoroughly with distilled water (4 × 500 ml).

Re-crystallization from ethyl acetate gives 3-nitroso-2-methyl-8-(2-phenylethenyl)-imidazo[1,2-a]pyridine, mp 158—160°C.

G. 3-Amino-2-methyl-8-(2-phenylethenyl)-imidazo[1,2-a]pyridine

To a stirred mixture of 3.0 g (0.01 mol) 3-nitroso-2-methyl-8-(2-phenylethenyl)-imidazo[1,2-a]pyridine in 50 ml of glacial acetic acid and 50 ml of water at 0°C. is added in portions 3.0 g (0.046 mol) zinc. When the addition is complete the mixture is stirred at 0°C for 1 hour. The mixture is filtered through celite; the filtrate is diluted with water and dichloromethane and basified at 10°C. with 80 ml of 5*N* sodium hydroxide. The resultant emulsion is filtered through a pad of celite and the celite pad is washed thoroughly with hot chloroform. The layers of the filtrate are separated and the aqueous phase is extracted with chloroform. The organic layer is washed with water and brine and dried over anhydrous sodium sulfate.

Following filtration, the chloroform is removed under reduced pressure to give 3-amino-2-methyl-8-(phenylethenyl)imidazo[1,2-a]pyridine. 1.0 g (0.004 mol) of the free base is dissolved in ethyl acetate and treated with 2 ml of 3.4M etheneal hydrogen chloride. Re-crystallization of the solid from methanol/ethyl acetate gives, 3-amino-2-methyl-8-(*trans*-2-phenylethenyl)-imidazo[1,2-a]pyridine hydrochloride, mp 241—250°C (dec.).

Example VIII

2-Methyl-3-isocyanomethyl-8-phenylmethoxy-imidazo[1,2-a]pyridine

2-Methyl-3-formylaminomethyl-8-phenylmethoxy-imidazo[1,2-a]pyridine 100 mg (0.29 mmol) is added to 6 ml dichloromethane containing 0.6 ml diisopropyl ethylamine and 0.1 ml phosphorous oxychloride. The mixture is stirred for 2 hours and diluted with water. The dichloromethane layer is separated, washed with saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulfate.

Following filtration the dichloromethane is removed under reduced pressure to give 2-methyl-3-isocyanomethyl-8-phenylmethoxyimidazo[1,2-a]pyridine, m.p.

Example IX

trans-2,3-Dimethyl-8-(2-phenylethenyl)-imidazo[1,2-a]pyridine hydrochloride.

A. 2,3-Dimethyl-8-formylimidazo[1,2-a]pyridine

A solution of 207 g (1.7 mol) 2-aminonicotinaldehyde and 300 g (2.0 mol) 3-bromo-2-butanone in 150 ml dichloromethane is heated on a steam bath allowing the solvent to distill and the mixture is maintained at 100—105°C for 2 hours.

The reaction mixture is dissolved in dilute hydrochloride acid and extracted with ether. The aqueous layer is neutralized with 20% sodium hydroxide. The solid precipitate is isolated by filtration and re-crystallized from ethyl acetate to give 2,3-dimethyl-8-formylimidazo[1,2-a]pyridine, mp 145—148°C.

B. *trans*-2,3-dimethyl-8-(2-phenylethenyl)imidazo[1,2-a]pyridine hydrochloride

A stirred solution of 116 g (0.51 mol) diethylbenzylphosphonate in 300 ml dimethylformamide is treated with 28 g (0.052 mol) sodium methoxide.

2,3-Dimethyl-8-formylimidazo[1,2-a]pyridine (80 g, 0.46 mol) is added in portions over 35 minutes while maintaining the temperature between 30—35°C. After stirring at room temperature 2.5 hours, the solvent is removed under reduced pressure and the residue portioned between 300 ml dichloromethane and 500 ml water.

The dichloromethane layer is separated and the solvent is removed under reduced pressure. The solid is triturated with ether (3 × 100 ml) and insolubles are removed from the ether solutions by filtration. The ether filtrates are combined and treated with ethereal hydrogen chloride. Re-crystallization of the solid from water gives *trans*-2,3-dimehyl-8-(2-phenylethenyl)-imidazo[1,2-a]pyridine, mp 240—255°C.

Example X

8-Benzyloxy-2,3-dimethylimidazo[1,2-a]pyridine

A. Mixture of 8-bromo- and 8-chloro-2,3-dimethylimidazo[1,2-a]pyridine

A stirred mixture of 6.38 g of 2-amino-3-chloro-pyrazine, 7.44 g of 3-bromo-2-butanone and 2.5 ml of anhydrous methanol in a bath maintained at 100° was heated for 18 hours. The mixture was cooled to room temperature and partitioned between aqueous sodium bicarbonate and methylene chloride. The layers were separated and the aqueous phase extracted with methylene chloride. The organic extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the residue was chromatographed on silica gel. A mixture of 8-chloro- and 8-bromo-2,3-dimethyl-imidazo[1,2-a]pyridine, m.p. 169.5°—172°C., was isolated upon crystallization of the residue from ethyl acetate.

B.

A solution of 3.13 g benzyl alcohol in 10 ml of dry dimethylformamide (DMF) was added to a stirred suspension of 1.39 g of 50% sodium hydride-mineral oil in 20 ml dry DMF and stirred at room temperature for two hours. A cooled (about 15°C) solution of 4.79 g of the product of Step A in 50 ml dry DMF was added and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated on a rotary evaporator under reduced pressure (55°C/0.2 torr.), and the residue was partitioned between water and methylene chloride.

Example XI

8-Benzyloxy-2-methyl-imidazo[1,2-a]pyrazine

A. 8-Chloro-2-methyl-imidazo[1,2-a]pyrazine

A mixture of 0.53 g of 2-amino-3-chloropyrazine and 0.84 g of 90% chloroacetone was heated at 100°C. for three hours. Then 0.41 g of triethylamine was added and the heating was continued for another 17 hours. Methylene chloride and aqueous sodium bicarbonate were added to the reaction mixture which was stirred vigorously. The organic and aqueous layers were separated and the aqueous phase extracted with methylene chloride. The organic extracts were combined, washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residual tar was stirred with 1:1 hexaneether. The insolubles were removed and the solvent evaporated under reduced pressure, yielding 8-chloro-2-methyl-imidazo[1,2-a]pyrazine, m.p. 127.5°—130°C.

B.

A solution of 1.84 g of benzyl alcohol in 10 mg dry DMF was added to a stirred suspension of 0.86 g of 50% sodium hydride-in-mineral oil in 5 ml of dry DMF and the mixtures stirred at room temperature for 30 minutes.

A cooled (ca. 10°—15°C.) solution of 2.60 g of 8-chloro-2-methyl-imidazo[1,2-a]pyrazine in 15 ml of dry DMF was added to the mixture, and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue triturated with ether and filtered to obtain 8-benzyloxy-2-methyl-imidazo[1,2-a]pyrazine, as determined by spectroscopic and combustion analysis, m.p. 99.5°—101.5°C.

Example XII

8-Benzyloxy-2-methyl-3-nitroso-imidazo[1,2-a]pyrazine

A solution of 14.2 g 2-methyl-8-phenylmethoxy-imidazo[1,2-a]pyrazine, 129.3 g n-butyl nitrite and 142 ml p-dioxane was heated under reflux for 0.5 hour and decanted from a small amount of gum. The supernatant solution was stirred under vacuum (40°/0.1 mm) and the residue azeotroped with cyclohexane to give 8-benzyloxy-2-methyl-3-nitroso-imidazo[1,2-a]pyrazine as a soft, green solid which was identified by pmr and ms.

Example XIII

3-Amino-8-benzyloxy-2-methyl-imidazo[1,2-a]pyrazine

8-Benzyloxy-2-methyl-3-nitroso-imidazo[1,2-a]pyrazine (18.3 g) was dissolved in 280 ml acetic acid and diluted using 140 ml water and the solution cooled to 18°C.; additional acetic acid (100 ml) was then added. Zinc powder (19.2 g) was added in portions over 10 minutes at 18—30°C. and then stirred 2 hours at room temperature.

The reaction mixture was concentrated *in vacuo* at 45°C. and the residue dissolved in 700 ml of a mixture of dichloromethane/water (5/2, V/V) and basified with 100 ml 2.5*M* sodium hydroxide. The resultant suspension was filtered through a celite pad, the filter cake washed with dichloromethane and the combined filtrate and washings separated. The aqueous layer was extracted with dichloromethane (3 × 100 ml) and the extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to leave a brown solid. Flash chromatography on silica gel using ethyl acetate gave 3-amino-8-benzyloxy-2-methyl-imidazo[1,2-a]pyrazine, m.p. 126.5—133°C.

Recrystallization from ethyl acetate gave an analytical sample, m.p. 134.5—136°C. Treatment of the free base with etheral hydrogen chloride gave 3-Amino-8-benzyloxy-2-methyl-imidazo[1,2-a]pyrazine hydrochloride, m.p. 119.5—120.5°C. (dec).

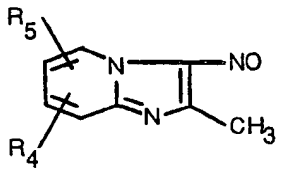
According to the processes outlined above, using the appropriate starting compounds, the following compounds may be obtained.

1. 2,3-Dimethyl-8-[1-E-(3-phenylpropenyl)]-imidazo[1,2-a]pyridine; (m.p. of hydrochloride salt: 201—204°C., dec.).
2. 2,3-Dimethyl-8-[(2-phenyl)-ethenyl]-imidazo[1,2-a]pyridine; (m.p. of hydrochloride methanolate (·HCl·CH_3OH): 243—255°C.)
3. 3-Cyanomethyl-2-methyl-8-[E-(2-phenyl-1-ethenyl)]-imidazo[1,2-a]pyridine; m.p. 133—136°C.
4. 3-Cyanomethyl-2-methyl-8-[E-1-(3-phenyl-propen-1-yl)]-imidazo[1,2-a]pyridine; m.p. 143—145.5°C.
5. 3-Cyanomethyl-2-methyl-6-(2-phenylethyl)-imidazo[1,2-a]pyridine; m.p. 139—141°C.
6. 3-Amino-8-benzyloxy-2-ethyl-imidazo[1,2-a]pyridine; m.p. 109—110°C.
7. 3-Amino-8-benzyloxy-2,7-dimethyl-imidazo[1,2-a]pyridine; m.p. of the hydrochloride monohydrate: 181—183°C.
8. 3-Amino-2-methyl-8-(2-phenylethyl)-imidazo[1,2-a]pyridine; m.p. of the hydrochloride including 1 mole methanol and 1/4 mol. H_2O: 74.5°C.
9. 3-Amino-2-methyl-8-(3-thienylmethoxy)-imidazo[1,2-a]pyridine; m.p. of hydrochloride: 187°C. (dec.)
10. 3-Dimethylamino-2-methyl-8-phenylmethoxy-imidazo[1,2-a]pyridine; m.p. of hydrochloride: 187°C. (dec.)
11. 3-Amino-8-benzyloxy-2,6-dimethyl-imidazo[1,2-a]pyridine; m.p. 141—142°C.
12. 8-Benzyloxy-3-ethylamino-2-methyl-imidazo[1,2-a]pyridine; m.p. of hydrochloride: 191°C. (dec.)
13. 3-Amino-2-methyl-8-[(3-thienylmethyl)-amino]-imidazo[1,2-a]pyridine; m.p. 161—163°C. (dec.)
14. 3-Amino-2-methyl-8-[Z-(2-phenylethenyl)]-imidazo[1,2-a]pyridine; m.p. of the 1/3 hydrate: 116—125°C.
15. 3-Amino-8-(4-chlorophenylmethoxy)-2-methyl-imidazo[1,2-a]pyridine; m.p. of the 1/4 hydrate: 156—158°C. (dec.)
16. 3-Amino-2-methyl-7-(2-phenylethyl)-imidazo[1,2-a]pyridine; m.p. 143—144°C.
17. 3-Amino-2-methyl-8-(2-thienylmethoxy)-imidazo[1,2-a]pyridine; m.p. of 2/3-hydrate: 147—149°C.
18. Trans-3-Amino-2,6-dimethyl-8-(2-phenylethenyl)-imidazo[1,2-a]pyridine; m.p. of hydrochloride: 273—275°C.
19. 3-Amino-8-(2-fluorophenylmethoxy)-2-methyl-imidazo[1,2-a]pyridine; m.p. of the 1/4 hydrate: 151—152.5°C.
20. 3-Amino-8-(4-fluorophenylmethoxy)-2-methyl-imidazo[1,2-a]pyridine; m.p. of 1/4 hydrate: 165—166°C.
21. 3-Amino-8-benzylamino-2-methyl-imidazo[1,2-a]pyridine; m.p. 145—155°C. (dec.)
22. 3-Amino-2-methyl-8-(2-phenylethenyl)-imidazo[1,2-a]pyridine; m.p. of hydrochloride with 2/3 mol. H_2O: Decomposition at 241—250°C.
23. 3-Amino-2-methyl-6-(2-phenylethyl)-imidazo[1,2-a]pyridine; m.p. 120—122°C.
24. 3-Amino-2-methyl-8-[E-1-(3-phenylpropen-1-yl)]-imidazo[1,2-a]pyridine; m.p. of hydrochloride: 222—224°C. (dec.)
25. 3-Ethylamino-2-methyl-8-(2-phenylethyl)-imidazo[1,2-a]pyridine; m.p. 145—147°C. (dec.)
26. 3-Amino-2,7-dimethyl-8-(2-phenylethyl)-imidazo[1,2-a]pyridine; m.p.
27. 8-Benzyloxy-3-isocyanomethyl-2-methyl-imidazo[1,2-a]pyridine; m.p.

Other typical compounds of this invention are listed in the Tables I to V below.

TABLE I

Compounds of the formula



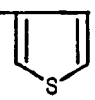
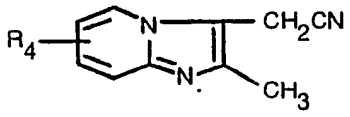
Compound No.	R_4	R_5	m.p. °C.
28.	(8)–O–CH_2– 	H	
29.	(8)–CH = CH– 	H	(dark green solid)
30.	(8)–CH_2–CH_2– 	H	131.5 — 132.5 (dec.)
31.	(6)–CH_2–CH_2– 	H	114 — 115 (dec.)
32.	(8)–O–CH_2– 	H	147.5 — 148.5 (dec.)
33.	(8)–O–CH_2– 	(7)—CH_3	118 — 120
34.	(8)–O–CH_2– 	H	120 — 122
35.	(7)–CH_2–CH_2– 	H	116 — 118 (dec.)
36.	(8)–CH = CH– 	H	158 — 160
37.	(8)–O–CH_2– 	H	133 — 134 (dec.)

TABLE II

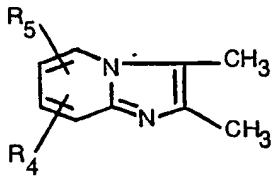
Compounds of formula



Compound No.	R_4	m.p. °C.
38.	(8)–CH = CH– 	134 — 136
39.	(5)–CH_2–CH_2– 	118 — 119
40.	(7)–CH_2–CH_2– 	118
41.	(8)–O–CH_2–CH = CH_2	177 — 179

TABLE III

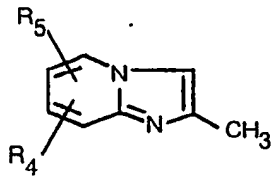
Compounds of formula



Compound No.	R_4	R_5	m.p. °C.
42.	(8)–CH = CH– 	(6)–CH_3	149 — 150
43.	cis (8)–CH = CH– 	H	174 — 177
43A.	trans (8)–CH = CH– 	H	240 — 225
44.	(7)–CH_2–CH_2– 	H	88 — 93
45.	(6)–CH_2–CH_2– 	H	105 — 107
46.	(5)–CH_2–CH_2– 	H	101 — 103
47.	(5)–O–CH_2– 	H	110
48.	(6)–CH_2– 	H	216 — 218

TABLE IV

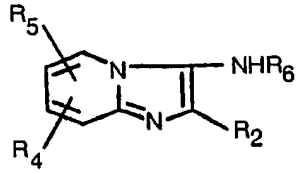
Compounds of formula



Compound No.	R_4	R_5	m.p. °C.
49.	(8)–CH = CH– 	(6)—CH_3	93 — 94
50.	(8)–CH = CH–  (cis)	H	(light yellow solid)
51.	(8)–CH = CH–  (trans)	H	100 — 102
52.	(6)–CH_2–CH_2– 	H	104 — 105
53.	(5)–CH_2–CH_2– 	H	86 — 88
54.	(8)–CH = CH–CH_2– 	H	73.5 — 78
55.	(5)–O–CH_2– 	H	(HCl-salt) 136.5 — 138.5
56.	(6)–O–CH_2– 	H	(HBr-salt) 228 — 230
57.	(7)–CH_2–CH_2– 	H	(.HCl.1/4 H_2O) 92 — 122

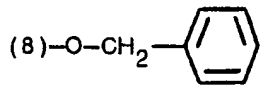
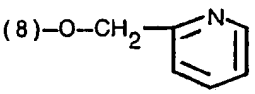
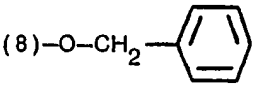
TABLE V

Compounds of formula



Compound No.	R_2	R_4	R_5	R_6	m.p. °C.
58	CH_3	(8)–O–CH_2–	H	H	(·H_2PO_4·1.33 H_2O) 214—215.5 dec.
59.	CH_3	(8)–O–CH_2–	H	CH_3	(·HCl·0.25 H_2O) 193.5 — 194
60.	$C(CH_3)_3$	(8)–O–CH_2–	H	H	173 — 175
61.	CH_3	(8)–O–CH_2–CH_2–	H	H	(·HCl·1/4 H_2O) 138 — 140 dec.
62.	CH_3	(5)–CH_2–CH_2–	H	H	(·HCl) 236 — 238
63.	CH_3	(8)–CH_2–CH_2–	(6)—CH_3	H	(·HCl) 218 — 220
64.	CH_3	(8)–O–CH_2–	(6)—Cl	H	157 — 158
65.	$CH_2CH_2CH_2CH_3$	(8)–O–CH_2–	H	H	115 — 117
66.	$CH(CH_3)_2$	(8)–O–CH_2–	H	H	167 — 169

TABLE V (Continued)

Compound No.	R_2	R_4	R_5	R_6	m.p. °C.
67.	$CH_2CH_2CH_3$		H	H	88 — 89
68.	CH_3		H	H	120 — 121 (dec.)
69.	H		H	H	(HCl) 209 — 210

Preferred imidazo[1,2-a]pyrazine compounds of this invention are:
8-benzyloxy-3-cyanomethyl-2-methyl-imidazo[1,2-a]pyrazine;
8-benzyloxy-2,3-dimethyl-imidazo[1,2-a]pyrazine;
3-amino-8-benzyloxy-2-methyl-imidazo[1,2-a]pyrazine; and
8-benzyloxy-3-ethylamino-2-methyl-imidazo[1,2-a]pyrazine.

The term "pharmaceutically acceptable salts" of this invention include salts wherein the acidic hydrogen forms an acid addition salt with an amine. (e.g. the phosphate salt of 3-amino-8-benzyloxy-2-methyl-imidazo[1,2-a]pyridine).

Suitable acids for the pharmaceutically acceptable acid addition salts include hydrochloric, sulfuric, phosphoric, nitric, acetic, propionic, maleic, ascorbic, citric and the like.

The acid addition salts are prepared via procedures well known in the art.

The compounds of this invention are useful in the treatment of peptic ulcers, having characteristics which enable the compounds to relieve the symptoms of peptic ulcer disease (including stress ulceration) and promote healing of gastic and/or duodenal ulcers. The anti-ulcer activity of the compounds of Formula I is identified by tests which measure their gastic antisecretory activity in the rat and dog and by tests which measure their cytoprotective effect (sometimes also referred to in the art as mucoprotective effect) in rats. The compounds are useful as conjunctive therapeutic agents for co-administration with such anti-inflammatory/analgesic agents as aspirin, indomethacin, phenylbutazones, ibuprofen, naproxen, tolmetin and other agents having the untoward side effect of contributing to damage to the gastrointestinal tract.

The compounds of this invention, in order to be evaluated for their applied use characteristics undergo testing procedures according to standard biological procedures wherein the compounds are evaluated both on an absolute basis and on a comparative basis with compounds known to possess the characteristics useful for the treatment and/or prevention of peptic ulcer disease, duodenal ulcer disease and drug induced gastric ulceration. Such tests include testing in dogs prepared under aseptic surgical conditions with either Heidenhain gastric pouches or simple gastric fitulas fitted to facilitate collection of gastric secretions. The test compounds are administered in appropriate and well-defined and well-known vehicles for either intravenous delivery or oral administration. The agonists employed to stimulate gastric secretion include such compounds as histamine, pentagastrin, and feeding in dogs equipped with Heidenhain pouches, and insulin hypoglycemia (in addition to histamine and pentagastrin) in dogs with gastric fistulas.

Caesarean-derived Sprague-Dawley male rats are used for gastric secretion with pyloric ligation techniques and anti-ulcer studies employing aspirin-induced ulceration.

From these and other tests, as well as by comparison with known anti-ulcer agents the compounds of this invention are found to be effective for the oral treatment of the ulcerative disease states herein mentioned at doses of about 0.5 to 50 mgm per kilogram of body weight per day, preferably being administered in 3—4 divided doses per day. In those instances wherein it is desired to administer the compounds of this invention via a parenteral route (e.g. intravenously) the compounds are administered at a dose range of about 0.01 to 10 mg/kg in single or multiple daily doses. Of course, the dose will be regulated by the attending diagnostician depending on factors such as the degree and severity of the disease state and age and general condition of the patient being treated. The recommended dose range for

the preferred compounds of this invention is the oral dose of 75 to 1600 mg/day in three to four divided doses to achieve relief of the symptoms of peptic ulcer disease and promote the healing of gastric and/or duodenal ulcers.

In their use in the treatment of peptic ulcer disease, gastic and duodenal ulcers, and in the prevention and treatment of drug-induced gastic ulceration, the compounds are administered in unit dosage forms such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, suppositories and the like. Such preparations are prepared according to standard techniques well-known in the art. A few examples of such pharmaceutical formulations are as follows.

Formulations

The following formulations are to exemplify some of the dosage forms in which the anti-ulcer agents of this invention may be employed. In each, the active ingredient is designated by the term "Drug" which is meant to indicate one of the following compounds:

3-amino-2-methyl-8-(2-phenylethyl)-imidazo[1,2-a]pyridine;
2,3-dimethyl-8-(2-phenylethenyl)-imidazo[1,2-a]pyridine;
3-cyanomethyl-2-methyl-8-[E-1-(3-phenyl-propen-1-yl)]-imidazo[1,2-a]pyridine;
8-benzyloxy-3-amino-2-methyl-imidazo[1,2-a]pyrazine; and
8-benzyloxy-2,3-dimethyl-imidazo[1,2-a]pyrazine.

It will be appreciated, however, that each of these compounds may be replaced by equally effective quantities of other compounds defined by Formula I and their pharmaceutically acceptable salts.

Formulation 1

Tablets

No.	Ingredient	mg/tab	mg/tab
1	Drug	25.0	400
2	Lactose impalpable powder USP	114	241.5
3	Corn starch USP	25.0	50.0
4	Corn starch as 5% paste in distilled water	10.0	35.0
5	Corn starch USP	25.0	50.0
6	Magnesium stearate USP	1.00	3.50
		200	780

Method of Manufacture

Mix items nos. 1, 2 and 3 in a suitable blender 5 to 15 minutes. Pass through a fine screen (#40) if necessary. Re-blend for 5 to 10 minutes and granulate with item no. 4. Pass the damp granulated mass through a coarse sieve (#6) using a suitable mill. Dry the damp granules at 40 to 50°C. overnight. Mill the dried granules using no. 20 screen. Add item no. 5 and blend for 5 to 10 minutes. Add item no. 6 and blend further for 3 to 5 minutes. Compress the tablet mixture into appropriate size and weight tablets with a suitable tabletting machine.

Formulation 2

Capsules

No.	Ingredient	mg/tab	mg/tab
1	Drug	25.0	400
2	Lactose, impalpable powder USP	144	191.5
3	Corn starch USP	30.0	105
4	Magnesium stearate USP	1.00	3.50
		200	700

Method of Manufacture

Mix items nos. 1, 2 and 3 in a suitable blender for 5 to 10 minutes. Pass through a fine screen (#40) if necessary. Re-blend for 5 to 10 minutes, add item no. 4 and mix further for 3 to 50 minutes. Using a suitable machine, encapsulate the mixture into a two-piece hard gelatin capsule of appropriate size.

Formulation 3

Suspensions

Ingredients	Formula A (mg/ml)	Formula B (mg/ml)
Drug	5.0	80.0
Sucrose	600.0	600.0
Benzyl alcohol	10.0	10.0
Methylcellulose (15 cps)	4.0	4.0
Polysorbte 80	5.0	5.0
Vanillin	0.2	0.2
Purified Water q.s.	1.0 ml	1.0 ml

Method of Manufacture

1. Charge approximately 40% of the final volume of purified water in a stainless steel tank. Heat to boiling. Agitate using an appropriate stirrer. Agitation should continue throughout procedure.
2. Add sucrose until it is dissolved.
3. Slowly add methylcellulose until it is well dispersed.
4. Start cooling the mixture to room temperature.
5. Add polysorbate, benzyl alcohol and vanillin until all ingredients are well dispersed.
6. Add the Drug until an uniform dispersion is formed.
7. This suspension is then q.s. to final volume with purified water at 25°C.

Formulation 4

Parenterals

	mg/ml
Drug	25.00
Methylparaben	1.30
Propylparaben	0.20
Sodium bisulfite	3.20
Disodium edetate	0.20
Sodium sulfate	2.60
Water for injection q.s. ad	1.0 ml

Method for Manufacture

1. Dissolve parabens in a portion (approximately 85% of the final volume) of the water for injection at 65—70°C.
2. Cool to 25—35°C. Charge and dissolve sodium bisulfite, disodium edetate and sodium sulfate.
3. Charge and dissolve the Drug.
4. Bring the solution to the final volume by adding water for injection.
5. Filter the solution through 0.22 μ membrane and fill into appropriate containers.
6. Terminally sterilize the units by autoclaving.

Formulation 5

Injectable Suspension

	mg/ml
Drug (Sterile)	50.0
Benzyl alcohol	9.0
Methylparaben	1.8
Propylparaben	0.2
Sodium carboxymethylcellulose	5.0
Polyethylene Glycol 4000	10.0
Povidone	5.0
Sodium Citrate	15.0
Disodium edetate	0.1
Water for injection	q.s.
To make	1.0 ml

Parenterals

Method of Preparation

1. Dissolve parabens in a portion of water for injection at 65—70°C.
2. Cool to 25—35°C. Charge and dissolve benzyl alcohol, sodium citrate, disodium edetate, PEG 4000, povidone and sodium carboxymethylcellulose.
3. Filter the solution and sterilize by autoclaving.
4. Make a slurry of the sterile active and pass it through a colloid mill.
5. Mix it well with solution from Step 3 and pass it through the mill.
6. Bring the suspension to the final volume/weight and fill into sterile containers.

Formulation 6

Suppositories

A. Formula	mg/supp
Drug	5.0
Cocoa butter	1995.0
	2.0 g.

Procedure

1. Melt cocoa butter to about 32—35°C.
2. Blend Drug into cocoa butter until well dispersed.
3. Pour into teflon-coated mould and congeal in refrigerator. Keep in refrigerator for an appropriate length of time.
4. Remove suppositories from mould.

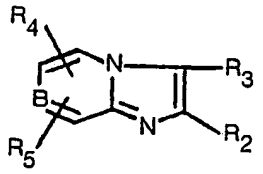
B. Formula	mg/supp
Drug	100.0
PEG 1000	1824.0
PEG 4000	76
	2.0 g.

Procedure

1. Melt PEG 1000 and PEG 4000 in one container to 50°C.
2. Add Drug to the mixture. Blend until well dispersed.
3. Pour into mould and congeal in refrigerator. Keep in refrigerator for an appropriate length of time.
4. Remove suppositories from mould.

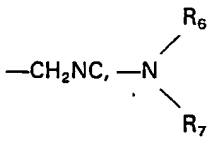
Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. Imidazo[1,2-a]pyridines and pyrazines of the general formula



I

wherein B is CH or N, whereby, when B is CH, then
R_2 is hydrogen, C_1—C_6 alkyl or hydroxy C_1—C_6 alkyl;
R_5 is hydrogen, halogen or C_1—C_6 alkyl; and either
R_3 is C_1—C_6 alkyl, —CH_2CN, hydroxy C_1—C_6 alkyl, —NO,



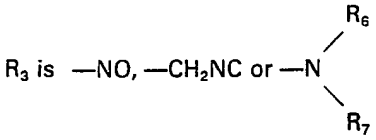
—CH_2NC, —N

or, provided R_2 is not hydrogen, also hydrogen and
R_4, being attached to any of the positions 5-, 6- or 7- of the nucleus, represents one of the groupings

—O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar, —CH=CH—CH_2—Ar or —O—CH_2—CH=CH_2; or

R_3 is as defined above and
R_4, being attached to the 8-position of the nucleus, represents any one of the groupings:

—CH=CH—Ar, —CH=CH—CH_2—Ar or —O—CH_2—CH=CH_2; or



R_3 is —NO, —CH_2NC or —N and

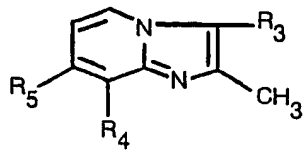
R_4, being attached to the 8-position of the nucleus, represents —O—R_8—Ar, —NH—R_8—Ar or —R_8—Ar; and when B is n, then
R_5 is as above defined,
R_2 and R_3 an independently selected from hydrogen, C_1—C_6 alkyl, hydroxy C_1—C_6 alkyl, —CH_2CN, —NO and —NR_6R_7 and
R_4 is —O—R_8—Ar, —NH—R_8—Ar, R_8—Ar, —CH=CH—Ar or —CH=CH—CH_2—Ar;
whereby, in the above definitions, R_6 and R_7 are independently selected from hydrogen or C_1—C_6 alkyl;
R_8 is a straight- or branched- chain C_1—C_6 alkylene group and
Ar represents thienyl, furanyl, pyridyl, phenyl or phenyl substituted by one or more substituents selected from halogen and C_1—C_6 alkyl;
the 2,3-dihydro; 5,6,7,8-tetrahydro and 2,3,5,6,7,8-hexahydro derivatives thereof and the pharmaceutically acceptable salts of such compounds.

2. Compounds of Formula I wherein B is CH,
R_2 represents —CH_3 or —CH_2CH_3;
R_5 represents hydrogen or —CH_3;
CH_3 represents —NH_2, —NHC_2H_5, —CH_2CN or —CH_3 and
R_4, being attached to the 5-, 6- or 7- position of the nucleus, represents —O—R_8—Ar, —NH-R_8—Ar, —R_8—Ar, —CH=CH—Ar or —CH=CH—CH_2—Ar with R_8 being methylene, ethylene or propylene and Ar being phenyl, o-fluorophenyl, p-fluorophenyl, p-chlorophenyl, thienyl or furanyl.

3. Compounds of Formula I wherein B, R_2 and R_5 are as defined in claim 2; R_4, being attached to the 8-position of the nucleus, is as defined in claim 2 and R_3 represents —NH_2 or —NHC_2H_5.

4. Compounds of Formula I wherein B, R_2 and R_5 are as defined in claim 2, R_3 is —CH_2CN or —CH_3 and R_4, being attached to the 8-position of the nucleus, is —CH=CH—Ar or —CH=CH—CH_2—Ar, with Ar being as defined in claim 2.

5. Compounds of the formula

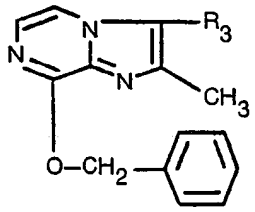


IA

wherein
R_3 is $-NH_2$;
R_4 is $-CH_2-CH_2-Ar$ or $-CH_2-CH_2-CH_2-Ar$ and
R_5 is hydrogen or methyl, whereby
Ar is phenyl or 3-thienyl.

6. Compounds of Formula IA set forth in claim 5, wherein
R_3 is $-NH_2$, $-CH_2CN$ or $-CH_3$
R_4 is $-CH=CH-Ar$ or $-CH=CH-CH_2-Ar$ and
R_5 is hydrogen or methyl, whereby
Ar is phenyl or 3-thienyl.

7. Compounds of the formula



wherein R_3 is C_1-C_6 alkyl, $-CH_2CN$, $-NH_2$ or $-NHC_2H_5$.

8. Compound according to claim 5, being 3-amino-2-methyl-8-(2-phenylethyl)-imidazo[1,2-a]pyridine.

9. Compounds according to claim 6, being 2,3-dimethyl-8-(2-phenyl-ethenyl)-imidazo[1,2-a]pyridine and 3-cyanomethyl-2-methyl-8-[E-1-(3-phenyl-propen-1-yl)]-imidazo[1,2-a]pyridine.

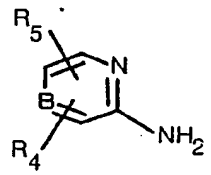
10. Compounds according to claim 7, being 8-benzyloxy-3-cyanomethyl-2-methyl-imidazo[1,2-a]pyrazine; 8-benzyloxy-2,3-dimethyl-imidazo[1,2-a]pyrazine and 3-amino-8-benzyloxy-2-methyl-imidazo[1,2-a]pyrazine.

11. Pharmaceutical compositions comprising a compound as defined in any one of claims 1 to 10.

12. Process for the preparation of pharmaceutical composition as defined in claim 11, characterized in that a compound as defined in any one of claims 1 to 10 is admixed with one or more suitable pharmaceutical carriers.

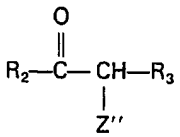
13. Process for the preparation of compounds as defined in any one of claims 1 to 10, characterized in that either

A: a compound of the general formula



II

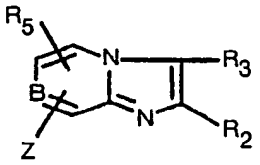
is reacted with a compound of the general formula



III

whereby, in the formulae, R_2, R_3, R_4 and R_5 are as defined in claim 1, except that any free amino or hydroxy groups present in R_2 or R_3 may be protected by a protecting group which is subsequently removed, and Z'' represents a good leaving group; or,

B: for preparation of compounds wherein R_4 is —O—R_8—Ar, —O—CH_2—CH=CH_2, —NH—R_8—Ar, —R_8—Ar, with R_8 and Ar being as defined in claim 1, a compound of the general formula



IV

is reacted with a compound of the general formula

Hal—Z′ V

whereby in the above formulae R_2, R_3 and R_5 are as defined in claim 1, Hal represents Br, Cl or J,

Z represents halogen, OH, or NH_2 and

Z′ represents —R_8—Ar or —CH_2—CH=CH_2.

C: for the preparation of a compounds wherein R_4 represents —CH=CH—Ar or —CH=CH—CH_2—Ar, a compound of Formula IV wherein R_2, R_3 and R_5 are as defined in claim 1 and Z represents CHO is subjected to a Wittig reaction with the appropriate Wittig reagent; or

D: for the preparation of compounds of Formula I wherein R_4 represents —CH=CH—Ar, reacting a compound of Formula IV wherein R_2, R_3, and R_5 are as defined in claim 1 and Z represents a phosphinylmethyl group, with a compound of formula Ar—CHO whereby Ar is as defined above; or

E: for the preparation of a compound of Formula I wherein R_2, R_4 and R_5 are as defined in claim 1 and R_3 represents CH_2CN, reacting a compound of Formula I wherein R_3 is a group —CH_2X, X being a good leaving group, with a metal cyanide; or

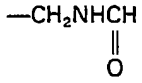
F: for the preparation of a compound of Formula I wherein R_2, R_3, R_4 and R_5 are as defined in claim 1, except that at least one of R_2 and R_3 must be hydroxy C_1—C_6 alkyl, reducing a compound of Formula I wherein R_2 and/or R_3 is a group —$(R')_nCOOR$, R′ being a C_1—C_6 alkylene group having 1 to 5 carbon atoms, n being zero or one and R being a hydrocarbon group; or

G: for the preparation of a compound of Formula I wherein R_2, R_4 and R_5 are as defined in claim 1 and R_3 is —NO, subjecting a compound of Formula I wherein R_3 is hydrogen to a nitrosation in the 3-position, or

H: for the preparation of compounds of Formula I wherein R_3 is —NH_2 and R_2, R_4 and R_5 are as defined in claim 1, reducing a compound of Formula I wherein R_3 is —NO or NO_2; or

I: for the preparation of a compound of Formula I wherein R_2, R_4 and R_5 are as defined in claim 1 and R_3 is —NR_6R_7 with R_6 and/or R_7 being C_1—C_6 alkyl, subjecting a compound of Formula I wherein R_3 is —NH_2 to an alkylation; or

J: for the preparation of a compound of Formula I wherein R_2, R_4 and R_5 are as defined in claim 1 and R_3 is —CH_2NC, subjecting a compound wherein R_3 is a group



to a reaction with PCl_3 in the presence of an amine;

that a so-obtained compound of Formula I, if desired, is reduced to the corresponding 2,3-dihydro, 5,6,7,8-tetrahydro- or 2,3,5,6,7,8-hexahydro derivative;

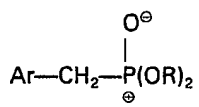
and that a compound obtained according to any one of the processes described above, if desired, is tranformed into a salt.

14. Process according to claim 13, characterized in that in process

A: Z″ represents halogen, tosyl or mesyl and the reaction is carried out by heating the reactants together in an inert solvent;

B: when Z represents halogen, a copper catalyst is used;

C: the Wittig reagent used is of the formula



with Ar being as defined in claim 1, R being a hydrocarbon group;

E: X represents halogen, alkoxy, aryloxy, mesyl, tosyl, a quaternary group, preferably $N^{\oplus}(CH_3)_3J^{\ominus}$, or a quaternary group wherein the quaternary ion is a non-nucleophilic counter ion selected from $BF^{\ominus}_4$, $PF^{\ominus}_6$, $CF_3SO^{\ominus}_3$, and $FSO^{\ominus}_3$ and the metal cyanide is an alkali metal cyanide;

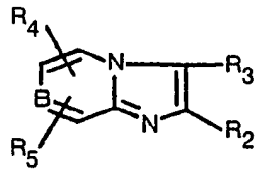
F: the reduction is carried out by means of lithium aluminium hydride;

G: the nitrosation is carried out by means of a nitrite, preferably sodium nitrite, in the presence of concentrated HCl;

H: the reduction is carried out by means of zinc powder in acetic acid.

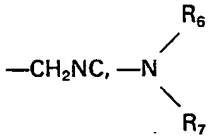
Claims for the Contracting State: AT

1. Process for the preparation of imidazo[1,2-a]pyridines and pyrazines of the general formula



I

wherein B is CH or N, whereby, when B is CH, then
R_2 is hydrogen, C_1—C_6 alkyl or hydroxy C_1—C_6 alkyl;
R_5 is hydrogen, halogen or C_1—C_6 alkyl; and either
R_3 is C_1—C_6 alkyl, —CH_2CN, hydroxy C_1—C_6 alkyl, —NO,



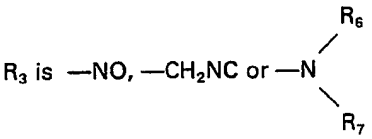
—CH_2NC, —N

or, provided R_2 is not hydrogen, also hydrogen and
R_4, being attached to any of the positions 5-, 6- or 7- of the nucleus, represents one of the groupings

—O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar, —CH=CH—CH_2—Ar or —O—CH_2—CH=CH_2; or

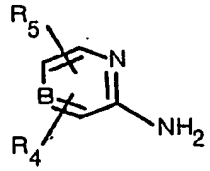
R_3 is as defined above and
R_4, being attached to the 8-position of the nucleus, represents any one of the groupings:

—CH=CH—Ar, —CH=CH—CH_2—Ar or —O—CH_2—CH=CH_2; or



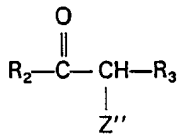
R_3 is —NO, —CH_2NC or —N and

R_4, being attached to the 8-position of the nucleus, represents —O—R_8—Ar, —NH—R_8—Ar or —R_8—Ar; and when B is n, then
R_5 is as above defined,
R_2 and R_3 an independently selected from hydrogen, C_1—C_6 alkyl, hydroxy C_1—C_6 alkyl, —CH_2CN, —NO and —NR_6R_7 and
R_4 is —O—R_8—Ar, —NH—R_8—Ar, R_8—Ar, —CH=CH—Ar or —CH=CH—CH_2—Ar;
whereby, in the above definitions, R_6 and R_7 are independently selected from hydrogen or C_1—C_6 alkyl;
R_8 is a straight- or branched- chain C_1—C_6 alkylene group and
Ar represents thienyl, furanyl, pyridyl, phenyl or phenyl substituted by one or more substituents selected from halogen and C_1—C_6 alkyl;
the 2,3-dihydro; 5,6,7,8-tetrahydro and 2,3,5,6,7,8-hexahydro derivatives thereof and the pharmaceutically acceptable salts of such compounds; characterized in that.
A: a compound of the general formula



II

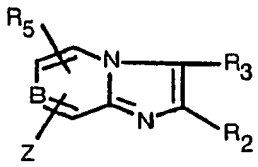
is reacted with a compound of the general formula



III

whereby, in the formulae, R_2, R_3, R_4 and R_5 are as defined in claim 1, except that any free amino or hydroxy groups present in R_2 or R_3 may be protected by a protecting group which is subsequently removed, and Z'' represents a good leaving group; or,

B: for preparation of compounds wherein R_4 is —O—R_8—Ar, —O—CH_2—CH=CH_2, —NH—R_8—Ar, —R_8—Ar, with R_8 and Ar being as defined in claim 1, a compound of the general formula



IV

is reacted with a compound of the general formula

Hal—Z' V

whereby in the above formulae R_2, R_3 and R_5 are as defined in claim 1, Hal represents Br, Cl or J,

Z represents halogen, OH, or NH_2 and

Z' represents —R_8—Ar or —CH_2—CH=CH_2.

C: for the preparation of a compounds wherein R_4 represents —CH=CH—Ar or —CH=CH—CH_2—Ar, a compound of Formula IV wherein R_2, R_3 and R_5 are as defined in claim 1 and Z represents CHO is subjected to a Wittig reaction with the appropriate Wittig reagent; or

D: for the preparation of compounds of Formula I wherein R_4 represents —CH=CH—Ar, reacting a compound of Formula IV wherein R_2, R_3, and R_5 are as defined in claim 1 and Z represents a phosphinylmethyl group, with a compound of formula Ar—CHO whereby Ar is as defined above; or

E: for the preparation of a compound of Formula I wherein R_2, R_4 and R_5 are as defined in claim 1 and R_3 represents CH_2CN, reacting a compound of Formula I wherein R_3 is a group —CH_2X, X being a good leaving group, with a metal cyanide; or

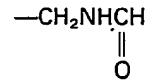
F: for the preparation of a compound of Formula I wherein R_2, R_3, R_4 and R_5 are as defined in claim 1, except that at least one of R_2 and R_3 must be hydroxyloweralkyl, reducing a compound of Formula I wherein R_2 and/or R_3 is a group —$(R')_nCOOR$, R' being a loweralkylene group having 1 to 5 carbon atoms, n being zero or one and R being a hydrocarbon group; or

G: for the preparation of a compound of Formula I wherein R_2, R_4 and R_5 are as defined in claim 1 and R_3 is —NO, subjecting a compound of Formula I wherein R_3 is hydrogen to a nitrosation in the 3-position, or

H: for the preparation of compounds of Formula I wherein R_3 is —NH_2 and R_2, R_4 and R_5 are as defined in claim 1, reducing a compound of Formula I wherein R_3 is —NO or NO_2; or

I: for the preparation of compounds of Formula I wherein R_2, R_4 and R_5 are as defined in claim 1 and R_3 is —NR_6R_7 with R_6 and/or R_7 being loweralkyl, subjecting a compound of Formula I wherein R_3 is —NH_2 to an alkylation; or

J: for the preparation of a compound of Formula I wherein R_2, R_4 and R_5 are as defined in claim 1 and R_3 is —CH_2NC, subjecting a compound wherein R_3 is a group



to a reaction with PCl_3 in the presence of an amine;

that a so-obtained compound of Formula I, if desired, is reduced to the corresponding 2,3-dihydro, 5,6,7,8-tetrahydro- or 2,3,5,6,7,8-hexahydro derivative;

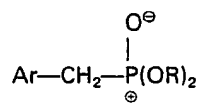
and that a compound obtained according to any one of the processes described above, if desired, is tranformed into a salt.

2. Process according to claim 1, characterized in that in process

A: Z'' represents halogen, tosyl or mesyl and the reaction is carried out by heating the reactants together in an inert solvent;

B: when Z represents halogen, a copper catalyst is used;

C: the Wittig reagent used is of the formula



with Ar being as defined in claim 1, R being a hydrocarbon group;

E: X represents halogen, alkoxy, aryloxy, mesyl, tosyl, a quaternary group, preferably $N^{\oplus}(CH_3)_3J^{\ominus}$, or a

quaternary group wherein the quaternary ion is a non-nucleophilic counter ion selected from $BF^{\ominus}_4$, $PF^{\ominus}_6$, $CF_3SO^{\ominus}_3$, and $FSO^{\ominus}_3$ and the metal cyanide is an alkali metal cyanide;

F: the reduction is carried out by means of lithium aluminium hydride;

G: the nitrosation is carried out by means of a nitrite, preferably sodium nitrite, in the presence of concentrated HCl;

H: the reduction is carried out by means of zinc powder in acetic acid.

3. Process according to claim 1 or 2, characterized in that compounds of Formula I wherein B is CH, R_2 represents $-CH_3$ or $-CH_2CH_3$;

R_5 represents hydrogen or $-CH_3$;

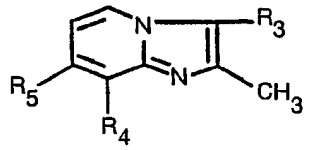
R_3 represents $-NH_2$, $-NHC_2H_5$, $-CH_2CN$ or $-CH_3$ and

R_4, being attached to the 5-, 6- or 7- position of the nucleus, represents $-O-R_8-Ar$, $-NH-R_8-Ar$, $-R_8-Ar$, $-CH=CH-Ar$ or $-CH=CH-CH_2-Ar$ with R_4 being methylene, ethylene or propylene and Ar being phenyl, o-fluorophenyl, p-fluorophenyl, p-chlorophenyl, thienyl or furanyl, are prepared.

4. Process according to claim 1 or 2, characterized in that compounds of Formula I wherein B, R_2 and R_5 are as defined in claim 3; R_4 being attached to the 8-position of the nucleus, is as defined in claim 3 and R_3 represents $-NH_2$ or $-NHC_2H_5$, are prepared..

5. Process according to claim 1 or 2, characterized in that compounds of Formula I wherein B, R_2 and R_5 are as defined in claim 3, R_3 is $-CHCN$ or $-CH_3$ and R_4, being attached to the 8-position of the nucleus, is $-CH=CH-Ar$ or $-CH=CH-CH_2-Ar$, with Ar being as defined in claim 3, are prepared.

6. Process according to claim 1 or 2, characterized in that compounds of the formula



IA

wherein

R_3 is $-NH_2$;

R_4 is $-CH_2-CH_2-Ar$ or $-CH_2-CH_2-CH_2-Ar$ and

R_5 is hydrogen or methyl, whereby

Ar is phenyl or 3-thienyl, are prepared.

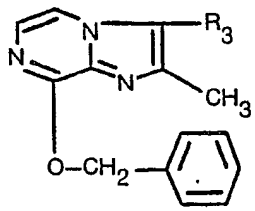
7. A process according to claim 1 or 2, characterized in that compounds of Formula IA set forth in claim 6, wherein

R_3 is $-NH_2$, $-CH_2CN$ or $-CH_3$

R_4 is $-CH=CH-Ar$ or $-CH=CH-CH_2-Ar$ and R_5 is hydrogen or methyl, whereby

Ar is phenyl or 3-thienyl, are prepared.

8. Process according to claim 1 or 2, characterized in that compounds of the formula



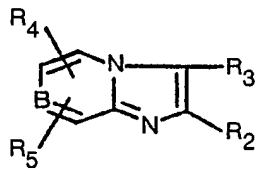
wherein R_3 is C_1-C_6 alkyl, $-CH_2CN$, $-NH_2$ or $-NHC_2Hs_5$, are prepared.

9. Process according to claim 1 or 2, characterized in that the compounds 3-amino-2-methyl-8-(2-phenylethyl)-imidazo[1,2-a]pyridine; 2,3-dimethyl-8-(2-phenyl-ethenyl)-imidazo[1,2-a]pyridine and 3-cyanomethyl-2-methyl-8-[E-1-(3-phenylpropen-1-yl)] imidazo[1,2-a]pyridine, are prepared.

10. Process according to claim 1 or 2, characterized in that the compounds 8-benzyloxy-3-cyanomethyl-2-methyl-imidazo[1,2-a]pyrazine; 8-benzyloxy-2,3-dimethyl-imdiazo[1,2-a]pyrazine and 3-amino-8-benzyloxy-2-methyl-imidazo[1,2-a]pyrazine are prepared.

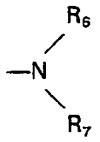
Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Imidazo[1,2-a]pyridine und -pyrazine der allgemeinen Formel

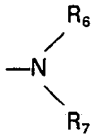


I

in der
B CH oder N ist, wobei, wenn B CH ist, dann
R_2 Wasserstoff, C_1—C_6-Alkyl oder Hydroxy-C_1—C_6-Alkyl ist;
R_5 Wasserstoff, Halogen oder C_1—C_6-Alkyl ist; und
entweder
R_3 C_1—C_6-Alkyl, —CH_2CN, Hydroxy-C_1—C_6-Alkyl, —NO, —CH_2NC,



oder, vorausgesetzt, daß R_2 nicht Wasserstoff ist, auch Wasserstoff ist und
R_4, gebunden in einer der Stellungen 5-, 6- oder 7- des Kerns, eine der Gruppierungen —O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar, —CH=CH—CH_2—Ar oder —O—CH_2—CH=CH_2 bezeichnet;
oder
R_3 die im Vorstehenden angegebene Bedeutung hat und
R_4, gebunden in der Stellung 8- des Kerns, irgendeine der Gruppierungen —CH=CH—Ar, —CH=CH—CH_2—Ar oder —O—CH_2—CH=CH_2 bezeichnet;
oder
R_3 NO, —CH_2NC oder



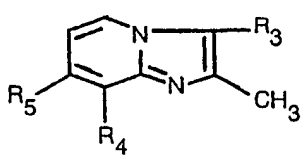
ist und
R_4 gebunden in der Stellung 8- des Kerns, —O—R_8—Ar, —NH—R_8—Ar oder —R_8—Ar bezeichnet, und
wenn B N ist, dann
R_5 die oben angegebenen Bedeutungen hat,
R_2 und R_3 unabhängig aus Wasserstoff, C_1—C_6-Alkyl, Hydroxy-C_1—C_6-Alkyl, —CH_2CN, —NO und —NR_6R_7 ausgewählt sind und
R_4 —O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar oder —CH=CH—CH_2—Ar ist;
wobei in den vorstehenden Definitionen
R_6 und R_7 unabhängig aus Wasserstoff oder C_1—C_6-Alkyl ausgewählt sind;
R_8 eine geradkettige oder ketennverzweigte C_1—C_6-Alkylen-Gruppe ist und
Ar Thienyl, Furanyl, Pyridyl, Phenyl oder durch einen oder mehrere, aus Halogen und C_1—C_6-Alkyl ausgewählte Substituenten substituiertes Phenyl bezeichnet;
deren 2,3-Dihydro-, 5,6,7,8-Tetrahydro- und 2,3,5,6,7,8-Hexahydro-Derivate und die pharmazeutisch annehmbaren Salze derartiger Verbindungen.

2. Verbindungen der Formel I, dadurch gekennzeichnet, daß B CH ist;
R_2 —CH_3 oder —CH_2CH_3 bezeichnet;
R_5 Wasserstoff oder —CH_3 bezeichnet;
R_3 —NH_2, —NHC_2H_5, —CH_2CN oder —CH_3 bezeichnet und
R_4, gebunden in der 5-, 6- oder 7-Stellung des Kerns, —O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar oder —CH=CH—CH_2—Ar bezeichnet, worin R_8 Methylen, Ethylen oder Propylen ist und Ar Phenyl, o-Fluorophenyl, p-Fluorophenyl, p-Chlorophenyl, Thienyl oder Furanyl ist.

3. Verbindungen der Formel I, dadurch gekennzeichnet, daß B, R_2 und R_5 die in Anspruch 2 angegebenen Bedeutungen haben, R_4, gebunden in der Stellung 8- des Kerns, die in Anspruch 2 angegebenen Bedeutungen hat und R_3 —NH_2 oder —NHC_3H_5 bezeichnet.

4. Verbindungen der Formel I, dadurch gekennzeichnet, daß B, R_2 und R_5 die in Anspruch 2 angegebenen Bedeugungen haben, R_3 —CH_2CN oder —CH_3 ist und R_4, gebunden in der Stellung 8- des Kerns, —CH=CH—Ar oder —CH=CH—CH_2—Ar ist, worin Ar die in Anspruch 2 angegebenen Bedeutungen hat.

5. Verbindungen der Formel



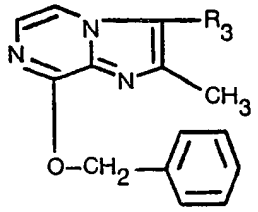
IA

in der
R_3 —NH_2 ist;
R_4 —CH_2—CH_2—Ar oder —CH_2—CH_2—CH_2—Ar ist und

R_5 Wasserstoff oder Methyl ist, worin
Ar Phenyl oder 3-Thienyl ist.

6. Verbindungen der Formel IA nach Anspruch 5, dadurch gekennzeichnet, daß
R_3 —NH_2, —CH_2CN oder —CH_3 ist;
R_4 —CH=CH—Ar oder —CH=CH—CH_2—Ar ist und
R_5 Wasserstoff oder Methyl ist, worin
Ar Phenyl oder 3-Thienyl ist.

7. Verbindungen der Formel



in der
R_3 C_1—C_6-Alkyl, —CH_2CN, —NH_2 oder —NHC_2H_5 ist.

8. Verbindung nach Anspruch 5, die 3-Amino-2-methyl-8-(2-phenylethyl)-imidazo[1,2-a]pyridin ist.

9. Verbindungen nach Anspruch 6, die 2,3 - Dimethyl - 8 - (2 - phenyl - ethenyl) - imidazo[1,2 - a]-pyridin und 3 - Cyanomethyl - 2 - methyl - 8 - [E - 1 - (3 - phenyl - propen - 1 - yl)]imidazo[1,2 - a]-pyridin sind.

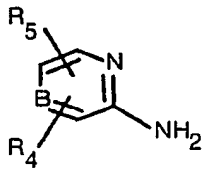
10. Verbindungen nach Anspruch 7, die 8 - Benzyloxy - 3 - cyanomethyl - 2 - methyl-]imidazo - [1,2 - a]pyrazin, 8 - Benzyloxy - 2,3 - dimethyl-]imidazo[1,2 - a]pyrazin und 3 - Amino - 8 - benzyloxy - 2 - methyl - imidazo[1,2 - a]pyrazin sind.

11. Pharmazeutische Zusammensetzungen, enthaltend eine Verbindung nach irgendeinem der Ansprüche 1 bis 10.

12. Verfahren zur Herstellung pharmazeutischer Zusammensetzungen nach Anspruch 11, dadurch gekennzeichnet, daß eine Verbindung nach irgendeinem der Ansprüche 1 bis 10 mit einem oder mehreren geeigneten pharmazeutischen Trägern vermischt wird.

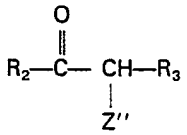
13. Verfahren zur Herstellung von Verbindungen nach irgendeinem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß entweder

A: eine Verbindung der allgemienen Formel



II

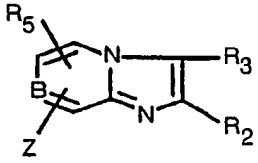
mit einer Verbindung der allgemeinen Formel



III

umgesetzt wird, wobei in den Formeln R_2, R_3, R_4 und R_5 die in Anspruch 1 angegebenen Bedeutungen haben, mit der Ausnahme, daß in R_2 oder R_3 vorhandene freie Amino- oder Hydroxy-Gruppen durch eine Schutzgruppe geschützt sein können, die anschließend entfernt wird, und Z'' eine leicht abspaltbare Gruppe bezeichnet, oder

B: zur Herstellung von Verbindungen, in denen R_4 —O—R_8—Ar, —O—CH_2—CH=CH_2, —NH—R_8—Ar, —R_8—Ar ist, worin R_8 und Ar die in Anspruch 1 angegebenen Bedeutungen haben, eine Verbindung der allgemeinen Formel



IV

mit einer Verbindung der allgemeinen Formel

Hal—Z'

umgesetzt wird, wobei in den vorstehenden Formeln R_2, R_3 und R_5 die in Anspruch 1 angegebenen Bedeutungen haben, Hal Br, Cl oder I bezeichnet, Z Halogen, OH oder NH_2 bezeichnet und Z' $—R_8—Ar$ oder $—CH_2—CH=CH_2$ bezeichnet,

C: zur Herstellung von Verbindungen der Formel I, in denen R_4 $—CH=CH—Ar$ oder $—CH=CH—CH_2—Ar$ bezeichnet, eine Verbindung der Formel IV, in der R_2, R_3 und R_5 die in Anspruch 1 angegebenen Bedeutungen haben und Z CHO bezeichnet, einer Wittig-Reaktion mit dem passenden Wittig-Reagens unterworfen wird; oder

D: zur Herstellung von Verbindungen der Formel I, in denen R_4 $—CH=CH—Ar$ bezeichnet, eine Verbindung der Formel IV, in der R_2, R_3 und R_5 die in Anspruch 1 angegebenen Bedeutungen haben und Z eine Phosphinylmethyl-Gruppe bezeichnet, mit einer Verbindung der Formel Ar—CHO, in der Ar die im Vorstehenden angegebene Bedeutung hat, umgesetzt wird; oder

E: zur Herstellung einer Verbindung der Formel I, in der R_2, R_4 und R_5 die in Anspruch 1 angegebenen Bedeutungen haben und R_3 CH_2CN bezeichnet, eine Verbindung der Formel I, in der R_3 eine Gruppe $—CH_2X$ bezeichnet, worin X eine leicht abspaltbare Gruppe bezeichnet, mit einem Metallcyanid umgesetzt wird; oder

F: zur Herstellung von Verbindungen der Formel I, in der R_2, R_3, R_4 und R_5 die in Anspruch 1 angegebenen Bedeutungen haben, jedoch mit der Ausnahme, daß wenigstens einer der Substituenten R_2 und R_3 Hydroxy-C_1—C_6-alkyl sein muß, eine Verbindung der Formel I, in der R_2 und/oder R_3 eine Gruppe $—(R')_nCOOR$ ist, worin R' eine C_1—C_6-Alkylen-Gruppe mit 1 bis 5 Kohlenstoff-Atomen ist, n 0 oder 1 ist und R eine Kohlenwasserstoff-Gruppe ist, reduziert wird; oder

G: zur Herstellung von Verbindungen der Formel I, in der R_2, R_4 und R_5 die in Anspruch 1 angegebenen Bedeutungen haben und R_3 $—NO$ bezeichnet, eine Verbindung der Formel I, in der R_3 Wasserstoff ist, einer Nitrosierung in der 3-Stellung unterworfen wird; oder

H: zur Herstellung von Verbindungen der Formel I, in der R_3 $—NH_2$ ist und R_2, R_4 und R_5 die in Anspruch 1 angegebenen Bedeutungen haben, eine Verbindung der Formel I, in der R_3 $—NO$ oder $—NO_2$ bezeichnet, reduziert wird; oder

I: zur Herstellung von Verbindungen der Formel I, in der R_2, R_4 und R_5 die in Anspruch 1 angegebenen Bedeutungen haben und R_3 $—NR_6R_7$ ist, worin R_6 und R_7 C_1—C_6-Alkyl sind, eine Verbindung der Formel I, in der R_3 $—NH_2$ ist, einer Alkylierung unterworfen wird; oder

J: zur Herstellung einer Verbindung der Formel I, in der R_2, R_4 und R_5 die in Anspruch 1 angegebenen Bedeutungen haben und R_3 CH_2NC bezeichnet, eine Verbindung der Formel I, in der R_3 eine Gruppe

$$—CH_2NHCH \overset{\|}{=} O$$

einer Reaktion mit PCl_3 in Gegenwart eines Amins unterworfen wird; daß eine auf diese Weise erhaltene Verbindung der Formel I gewünschtenfalls zu dem entsprechenden 2,3-Dihydro-, 5,6,7,8-Tetrahydro oder 2,3,5,6,7,8-Hexahydro-Derivat reduziert wird; und daß eine nach irgendeinem der im Vorstehenden beschriebenen Verfahren hergestellte Verbindung gewünschtenfalls in ein Salz überführt wird.

14. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß in dem Verfahren

A: Z'' Halogen, Tosyl oder Mesyl bezeichnet und die Reaktion durch gemeinsames Erhitzen der Reaktionspartner in einem inerten Lösungsmittel durchgeführt wird;

B: wenn Z Halogen bezeichnet, ein Kupfer-Katalysator verwendet wird;

C: das verwendete Wittig-Reagens die Formel

$$Ar—CH_2—\overset{\oplus}{P}(OR)_2 \quad (O^{\ominus})$$

besitzt, in der Ar die in Anspruch 1 angegebene Bedeutung hat und R eine Kohlenwasserstoff-Gruppe ist;

E: X Halogen, Alkyloxy, Aryloxy, Mesyl, Tosyl, eine quaternäre Gruppe, vorzugsweise $\overset{\oplus}{N}(CH_3)_3\ I^{\ominus}$, oder eine quaternäre Gruppe, in der das quaternäre Ion ein nicht-nucleophiles Gegenion ausgewählt aus $BF_4^{\ominus}$, $PF_6^{\ominus}$, $CF_3SO_3^{\ominus}$ und $FSO_3^{\ominus}$ ist, bezeichnet, und das Metallcyanid ein Alkalimetallcyanid ist;

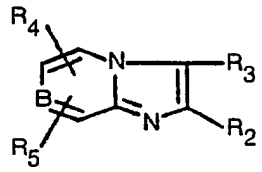
F: die Reduktion mit Hilfe von Lithiumaluminiumhydrid durchgeführt wird;

G: die Nitrosierung mit Hilfe eines Nitrits, vorzugsweise von Natriumnitrit, in Gegenwart konzentrierter HCl durchgeführt wird;

H: die Reduktion mit Hilfe von Zink-Pulver in Essigsäure durchgeführt wird.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung von Imidazo[1,2-a]pyridinen und -pyrazinen der allgemeinen Formel



I

in der

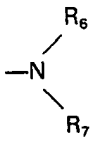
B CH oder N ist, wobei, wenn B CH ist, dann

R_2 Wasserstoff, C_1—C_6-Alkyl oder Hydroxy-C_1—C_6-Alkyl ist;

R_5 Wasserstoff, Halogen oder C_1—C_6-Alkyl sit; und

entweder

R_3 C_1—C_6-Alkyl, —CH_2CN, Hydroxy-C_1—C_6-Alkyl, —NO, —CH_2NC,



oder, vorausgesetzt, daß R_2 nicht Wasserstoff ist, auch Wasserstoff ist und

R_4, gebunden in einer der Stellungen 5-, 6- oder 7- des Kerns, eine der Gruppierungen —O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar, —CH=CH—CH_2—Ar oder —O—CH_2—CH=CH_2 bezeichnet;

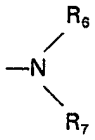
oder

R_3 die im Vorstehenden angegebene Bedeutung hat und

R_4, gebunden in der Stellung 8- des Kerns, irgendeine der Gruppierungen —CH=CH—Ar, —CH=CH—CH_2—Ar oder —O—CH_2—CH=CH_2 bezeichnet;

oder

R_3 NO, —CH_2NC oder



ist und

R_4 gebunden in der Stellung 8- des Kerns, —O—R_8—Ar, —NH—R_8—Ar oder —R_8—Ar bezeichnet, und

wenn B N ist, dann

R_5 die oben angegebenen Bedeutungen hat,

R_2 und R_3 unabhängig aus Wasserstoff, C_1—C_6-Alkyl, Hydroxy-C_1—C_6-Alkyl, —CH_2CN, —NO und —NR_6R_7 ausgewählt sind und

R_4 —O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar oder —CH=CH—CH_2—Ar ist;

wobei in den vorstehenden Definitionen

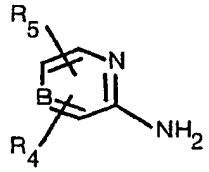
R_6 und R_7 unabhängig aus Wasserstoff oder C_1—C_6-Alkyl ausgewählt sind;

R_8 eine geradkettige oder kentenverzweigte C_1—C_6-Alkylen-Gruppe ist und

Ar Thienyl, Furanyl, Pyridyl, Phenyl oder durch einen oder mehrere, aus Halogen und C_1—C_6-Alkyl ausgewählte Substituenten substituiertes Phenyl bezeichnet;

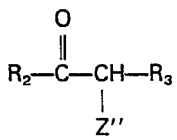
deren 2,3-Dihydro-, 5,6,7,8-Tetrahydro- und 2,3,5,6,7,8-Hexahydro-Derivaten und den pharmazeutisch annehmbaren Salze derartiger Verbindungen, dadurch gekennzeichnet, daß

A: eine Verbindung der allgemienen Formel



II

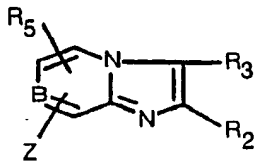
mit einer Verbindung der allgemeinen Formel



III

umgesetzt wird, wobei in den Formeln R_2, R_3, R_4 und R_5 die im Vorstehenden angegebenen Bedeutungen haben, mit der Ausnahme, daß in R_2 oder R_3 vorhandene freie Amino- oder Hydroxy-Gruppen durch eine Schutzgruppe geschützt sein können, die anschließend entfernt wird, und Z'' eine leicht abspaltbare Gruppe bezeichnet, oder

B: zur Herstellung von Verbindungen, in denen R_4 —O—R_8—Ar, —O—CH_2—CH=CH_2, —NH—R_8—Ar, —R_8—Ar ist, worin R_8 und Ar die im Vorstehenden angegebenen Bedeutungen haben, eine Verbindung der allgemeinen Formel



IV

mit einer Verbindung der allgemeinen Formel

Hal—Z'

umgesetzt wird, wobei in den vorstehenden Formeln R_2, R_3 und R_5 die im Vorstehenden angegebenen Bedeutungen haben, Hal Br, Cl oder I bezeichnet, Z Halogen, OH oder NH_2 bezeichnet und Z' —R_8—Ar oder —CH_2—CH=CH_2 bezeichnet,

C: zur Herstellung von Verbindungen der Formel I, in denen R_4 —CH=CH—Ar oder —CH=CH—CH_2—Ar bezeichnet, eine Verbindung der Formel IV, in der R_2, R_3 und R_5 die im Vorstehenden angegebenen Bedeutungen haben und Z CHO bezeichnet, einer Wittig-Reaktion mit dem passenden Wittig-Reagens unterworfen wird; oder

D: zur Herstellung von Verbindungen der Formel I, in denen R_4 —CH=CH—Ar bezeichnet, eine Verbindung der Formel IV, in der R_2, R_3 und R_5 die im Vorstehenden angegebenen Bedeutungen haben und Z eine Phosphinylmethyl-Gruppe bezeichnet, mit einer Verbindung der Formel Ar—CHO, in der Ar die im Vorstehenden angegebene Bedeutung hat, umgesetzt wird; oder

E: zur Herstellung einer Verbindung der Formel I, in der R_2, R_4 und R_5 die im Vorstehenden angegebenen Bedeutungen haben und R_3 CH_2CN bezeichnet, eine Verbindung der Formel I, in der R_3 eine Gruppe —CH_2X bezeichnet, worin X eine leicht abspaltbare Gruppe bezeichnet, mit einem Metallcyanid umgesetzt wird; oder

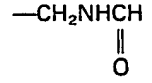
F: zur Herstellung von Verbindungen der Formel I, in der R_2, R_3, R_4 und R_5 die im Vorstehenden angegebenen Bedeutungen haben, jedoch mit der Ausnahme, daß wenigstens einer der Substituenten R_2 und R_3 Hydroxy-C_1—C_6-alkyl sein muß, eine Verbindung der Formel I, in der R_2 und/oder R_3 eine Gruppe —$(R')_n$COOR ist, worin R' eine C_1—C_6-Alkylen-Gruppe mit 1 bis 5 Kohlenstoff-Atomen ist, n 0 oder 1 ist und R eine Kohlenwasserstoff-Gruppe ist, reduziert wird; oder

G: zur Herstellung von Verbindungen der Formel I, in der R_2, R_4 und R_5 die im Vorstehenden angegebenen Bedeutungen haben und R_3 —NO bezeichnet, eine Verbindung der Formel I, in der R_3 Wasserstoff ist, einer Nitrosierung in der 3-Stellung unterworfen wird; oder

H: zur Herstellung von Verbindungen der Formel I, in der R_3 —NH_2 ist und R_2, R_4 und R_5 die im Vorstehenden angegebenen Bedeutungen haben, eine Verbindung der Formel I, in der R_3 —NO oder —NO_2 bezeichnet, reduziert wird; oder

I: zur Herstellung von Verbindungen der Formel I, in der R_2, R_4 und R_5 die im Vorstehenden angegebenen Bedeutungen haben und R_3 —NR_6R_7 ist, worin R_6 und R_7 C_1—C_6-Alkyl sind, eine Verbindung der Formel I, in der R_3 —NH_2 ist, einer Alkylierung unterworfen wird; oder

J: zur Herstellung einer Verbindung der Formel I, in der R_2, R_4 und R_5 die im Vorstehenden angegebenen Bedeutungen haben und R_3 CH_2NC bezeichnet, eine Verbindung der Formel I, in der R_3 eine Gruppe



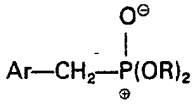
einer Reaktion mit PCl_3 in Gegenwart eines Amins unterworfen wird; daß eine auf diese Weise erhaltene Verbindung der Formel I gewünschtenfalls zu dem entsprechenden 2,3-Dihydro-, 5,6,7,8-Tetrahydro oder 2,3,5,6,7,8-Hexahydro-Derivat reduziert wird; und daß eine nach irgendeinem der im Vorstehenden beschriebenen Verfahren hergestellte Verbindung gewünschtenfalls in ein Salz überführt wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß in dem Verfahren

A: Z'' Halogen, Tosyl oder Mesyl bezeichnet und die Reaktion durch gemeinsames Erhitzen der Reaktionspartner in einem inerten Lösungsmittel durchgeführt wird;

B: wenn Z Halogen bezeichnet, ein Kupfer-Katalysator verwendet wird;

C: das verwendete Wittig-Reagens die Formel



besitzt, in der Ar die in Anspruch 1 angegebene Bedeutung hat und R eine Kohlenwasserstoff-Gruppe ist;

E: X Halogen, Alkyloxy, Aryloxy, Mesyl, Tosyl, eine quaternäre Gruppe, vorzugsweise $\overset{\oplus}{N}(CH_3)_3\ I^{\ominus}$, oder eine quaternäre Gruppe, in der das quaternäre Ion ein nicht-nucleophiles Gegenion ausgewählt aus $BF_4^{\ominus}$, $PF_6^{\ominus}$, $CF_3SO_3^{\ominus}$ und $FSO_3^{\ominus}$ ist, bezeichnet, und das Metallcyanid ein Alkalimetallcyanid ist;

F: die Reduktion mit Hilfe von Lithiumaluminiumhydrid durchgeführt wird;

G: die Nitrosierung mit Hilfe eines Nitrits, vorzugsweise von Natriumnitrit, in Gegenwart konzentrierter HCl durchgeführt wird;

H: die Reduktion mit Hilfe von Zink-Pulver in Essigsäure durchgeführt wird.

3. Verfahren nach Ansprüchen 1 oder 2, dadurch gekennzeichnet, daß Verbindungen der Formel I, in der B CH ist;

R_2 $-CH_3$ oder $-CH_2CH_3$ bezeichnet;

R_5 Wasserstoff oder $-CH_3$ bezeichnet;

R_3 $-NH_2$, $-NHC_2H_5$, $-CH_2CN$ oder $-CH_3$ bezeichnet und

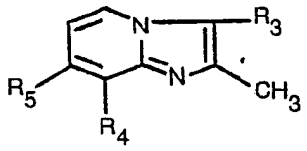
R_4, gebunden in der 5-, 6- oder 7-Stellung des Kerns, $-O-R_8-Ar$, $-NH-R_8-Ar$, $-R_8-Ar$, $-CH=CH-Ar$ oder $-CH=CH-CH_2-Ar$ bezeichnet, worin R_8 Methylen, Ethylen oder Propylen ist und Ar Phenyl, o-Fluorophenyl, p-Fluorophenyl, p-Chlorophenyl, Thienyl oder Furanyl ist,

hergestellt werden.

4. Verfahren nach Ansprüchen 1 oder 2, dadurch gekennzeichnet, daß Verbindungen der Formel I, in der B, R_2 und R_5 die in Anspruch 3 angegebenen Bedeutungen haben, R_4, gebunden in der Stellung 8- des Kerns, die in Anspruch 3 angegebenen Bedeutungen hat und R_3 $-NH_2$ oder $-NHC_2H_5$ bezeichnet, hergestellt werden.

5. Verfahren nach Ansprüchen 1 oder 2 dadurch gekennzeichnet, daß Verbindungen der Formel I, in der B, R_2 und R_5 die in Anspruch 3 angegebenen Bedeutungen haben, R_3 $-CH_2CN$ oder $-CH_3$ ist und R_4, gebunden in der Stellung 8- des Kerns, $-CH=CH-Ar$ oder $-CH=CH-CH_2-Ar$ ist, worin Ar die in Anspruch 3 angegebenen Bedeutungen hat, hergestellt werden.

6. Verfahren nach Ansprüchen 1 oder 2, dadurch gekennzeichnet, daß Verbindungen der Formel



IA

in der

R_3 $-NH_2$ ist;

R_4 $-CH_2-CH_2-Ar$ oder $-CH_2-CH_2-CH_2-Ar$ ist und

R_5 Wasserstoff oder Methyl ist, worin

Ar Phenyl oder 3-Thienyl ist,

hergestellt werden.

7. Verfahren nach Ansprüchen 1 oder 2, dadurch gekennzeichnet, daß Verbindungen der Formel IA nach Anspruch 5, dadurch gekennzeichnet, daß

R_3 $-NH_2$, $-CH_2CN$ oder $-CH_3$ ist;

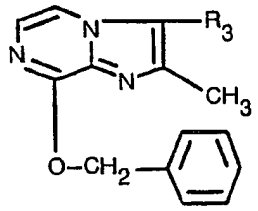
R_4 $-CH=CH-Ar$ oder $-CH=CH-CH_2-Ar$ ist und

R_5 Wasserstoff oder Methyl ist, worin

Ar Phenyl oder 3-Thienyl ist,

hergestellt werden.

8. Verfahren nach Ansprüchen 1 oder 2, dadurch gekennzeichnet, daß Verbindungen der Formel



in der

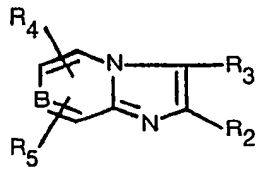
R_3 C_1—C_6-Alkyl, $-CH_2CN$, $-NH_2$ oder $-NHC_2H_5$ ist, hergestellt werden.

9. Verfahren nach Ansprüchen 1 oder 2, dadurch gekennzeichnet, daß die Verbindungen, 3 - Amino - 2 - methyl - 8 - (2 - phenylethyl) - imidazo[1,2 - a]pyridin, 2,3 - Dimethyl - 8 - (2 - phenyl - ethenyl) - imidazo[1,2 - a]pyridin und 3 - Cyanomethyl - 2 - methyl - 8 - [E - 1 - (3 - phenyl - propen - 1 - yl)] - imidazo[1,2 - a]pyridin hergestellt werden.

10. Verfahren nach Ansprüchen 1 oder 2, dadurch gekennzeichnet, daß die Verbindung, 8 - Benzyloxy - 3 - cyanomethyl - 2 - methyl-]imidazo[1,2 - a]pyrazin, 8 - Benzyloxy - 2,3 - dimethyl-] - imidazo[1,2 - a]pyrazin und 3 - Amino - 8 - benzyloxy - 2 - methyl - imidazo[1,2 - a]pyrazin hergestellt werden.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Imidazo[1,2-a]pyridines et pyrazines de formule générale



I

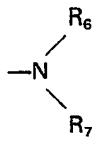
où B est CH ou N, et quand B est CH, alors

R_2 est hydrogène, alcoyle C_1—C_6 ou hydroxyalcoyle C_1—C_6;

R_5 est hydrogène, halogène ou alcoyle C_1—C_6;

et *soit*

R_3 est alcoyle C_1—C_6, —CH_2CN, hydroxyalcoyle C_1—C_6, —NO, —CH_2NC,



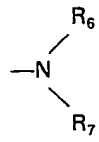
ou, à condition que R_2 ne soit pas de l'hydrogène, également de l'hydrogène et

R_4, étant attaché à toute position 5-, 6- ou 7- du noyau, représente l'un des groupements —O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar, —CH=CH—CH_2—Ar ou —O—CH_2—CH=CH_2; ou

R_3 est tel que défini ci-dessus et

R_4, étant attaché à la position 8 du noyau, représente l'un des groupements: —CH=CH—Ar, —CH=CH—CH_2—Ar ou —O—CH_2—CH=CH_2; ou

R_3 est —NO, —CH_2NC ou



et

R_4, étant attaché à la position 8 du noyau, représente —O—R_8—Ar, —NH—R_8—Ar ou —R_8—Ar;

et quand B est N, alors

R_5 est tel que défini ci-dessus,

R_2 et R_3 sont indépendamment choisis parmi l'hydrogène, un alcoyle C_1—C_6, un hydroxyalcoyle C_1—C_6, —CH_2CN, —NO et —NR_6R_7 et

R_4 est —O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar ou —CH=CH—CH_2—Ar;

et dans les définitions ci-dessus, R_6 et R_7 sont indépendamment choisis parmi l'hydrogène ou un alcoyle C_1—C_6;

R_8 est un groupe alcoylène C_1—C_6 à chaîne droite ou ramifiée et

Ar représente thiényle, furanyle, pyridyle, phényle ou phényle substitué par un ou plusieurs substituants choisis parmi un halogène et un alcoyle C_1—C_6;

leurs dérivés 2,3-dihydro; 5,6,7,8-tétrahydro et 2,3,5,6,7,8-hexahydro et les sels acceptables en pharmacie de tels composés.

2. Composés de formule I où B est CH,

R_2 représente —CH_3 ou —CH_2CH_3;

R_5 représente de l'hydrogène ou —CH_3;

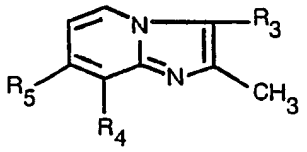
R_3 représente —NH_2, —NHC_2H_5, —CH_2CN ou —CH_3 et

R_4, étant attaché à la position 5-, 6- ou 7- du noyau, représente —O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar ou —CH=CH—CH_2—Ar, avec R_8 étant méthylène, éthylène ou propylène et Ar étant phényle, o-fluorophényle, p-fluorophényle, p-chlorophényle, thiényle ou furanyle.

3. Composés de formule I où B, R_2 et R_5 sont tels que définis à la revendication 2; R_4, étant attaché à la position 8 du noyau, est tel que défini à la revendication 2 et R_3 représente —NH_2 ou —NHC_2H_5.

4. Composés de formule I où B, R_2 et R_5 sont tels que définis à la revendication 2, R_3 est —CH_2CN ou —CH_3 et R_4, étant attaché à la position 8 du noyau, est —CH=CH—Ar ou —CH=CH—CH_2—Ar, Ar étant tel que défini à la revendication 2.

5. Composés de formule



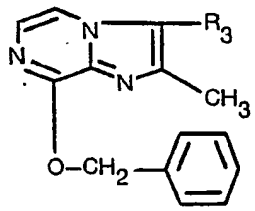
IA

où

R_3 est —NH_2;
R_4 est —CH_2—CH_2—Ar ou —CH_2—CH_2—CH_2—Ar et
R_5 est hydrogène ou méthyle, et
Ar est phényle ou 3-thiényle.

6. Composés de formule IA indiquée à la revendication 5, où
R_3 est —NH_2, —CH_2CN ou —CH_3
R_4 est —CH=CH—Ar ou —CH=CH—CH_2—Ar et
R_5 est hydrogène ou méthyle, et
Ar est phényle ou 3-thiényle.

7. Composés de formule



où

R_3 est alcoyle C_1—C_6, —CH_2CN, —NH_2, ou —NHC_2H_5.

8. Composé selon la revendication 5, étant la 3 - amino - 2 - méthyl - 8 - (2 - phényléthyl) - imidazo-[1,2 - a]pyridine.

9. Composés selon la revendication 6, étant la 2,3 - diméthyl - 8 - (2 - phényl - éthényl) - imidazo-[1,2 - a]pyridine et la 3 - cyanométhyl - 2 - méthyl - 8 - [E - 1 - (3 - phényl - propén - 1 - yl)] - imidazo-[1,2 - a]pyridine.

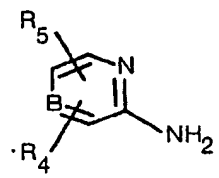
10. Composés selon la revendication 7, étant la 8 - benzyloxy - 3 - cyanométhyl - 2 - méthyl - imidazo[1,2 - a]pyrazine; la 8 - benzyloxy - 2,3 - diméthyl - imidazo[1,2 - a]pyrazine; et la 3 - amino - 8 - benzyloxy - 2 - méthyl - imidazo[1,2 - a]pyrazine.

11. Compositions pharmaceutiques comprenant un composé tel que défini selon l'une des revendications 1 à 10.

12. Procédé pour la préparation d'une composition pharmaceutique telle que définie à la revendication 11, caractérisé en ce qu'un composé tel que défini selon l'une des revendications 1 à 10 est mélangé à un ou plusieurs véhicules pharmaceutiques appropriés.

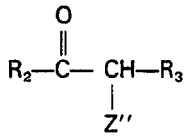
13. Procédé pour la préparation de composés tels que définis selon l'une des revendications 1 à 10, caractérisé en ce que soit

A: on fait réagir un composé de formule générale



II

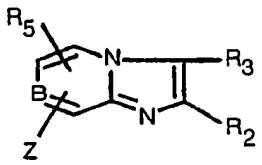
avec un composé de formule générale



III

et dans les formules, R_2, R_3, R_4 et R_5 sont tels que définis à la revendication 1, à l'exception que tout groupe amino ou hydroxy libre présent dans R_2 et R_3 peut être protégé par un groupe protecteur qui est subséquemment retiré et Z'' représente un bon groupe partant; ou

B: pour la préparation de composés où R_4 est —O—R_8—Ar, —O—CH_2—CH=CH_2, —NH—R_8—Ar, —R_8—Ar, avec R_8 et Ar étant tels que définis à la revendication 1, on fait réagir un composé de formule générale



IV

avec un composé de formule générale

Hal—Z' V

et dans les formules ci-dessus, R_2, R_3 et R_5 sont tels que définis à la revendication 1, Hal représente Br, Cl ou I,

Z représente un halogène, OH ou NH_2 et

Z' représente —R_8—Ar ou CH_2—CH=CH_2.

C: pour la préparation de composés où R_4 représente —CH=CH—Ar ou —CH=CH—CH_2—Ar, un composé de formule IV où R_2, R_3 et R_5 sont tels que définis à la revendication 1 et Z représente CHO est soumis à une réaction de Wittig avec le réactif approprié de Wittig; ou

D: pour la préparation de composés de formule I où R_4 représente —CH=CH—Ar, la réaction d'un composé de formule IV où R_2, R_3 et R_5 sont tels que définis à la revendication 1 et Z représente un groupe phosphinylméthyle, avec un composé de formule Ar-CHO dans lequel Ar est tel que défini ci-dessus; ou

E: pour la préparation d'un composé de formule I où R_2, R_4 et R_5 sont tels que définis à la revendication 1 et R_3 représente CH_2CN, la réaction d'un composé de formule I où R_3 est un groupe —CH_2X, X étant un bon groupe partant, avec un cyanure de métal; ou

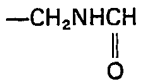
F: pour la préparation de composés de formule I où R_2, R_3, R_4 et R_5 sont tels que définis à la revendication 1, à l'exception qu'au moins l'un de R_2 et R_3 doit être un hydroxyalcoyle C_1—C_6, la réduction d'un composé de formule I où R_2 et/ou R_3 est un groupe —$(R')_nCOOR$, R' étant un groupe alcoylène C_1—C_6 ayant 1 à 5 atomes de carbone, n étant zéro ou un et R étant un groupe hydrocarbure; ou

G: pour la préparation de composés de formule I où R_2, R_4 et R_5 sont tels que définis à la revendication 1 et R_3 est —NO, la soumission d'un composé de formule I où R_3 est de l'hydrogène à une nitrosation, à la position 3, ou

H: pour la préparation de composés de formule I où R_3 est —NH_2 et R_2, R_4 et R_5 sont tels que définis à la revendication 1, la réduction d'un composé de formule I où R_3 est —NO ou NO_2; ou

I: pour la préparation de composés de formule I où R_2, R_4 et R_5 sont tels que définis à la revendication 1 et R_3 est —NR_6R_7 avec R_6 et/ou R_7 étant un alcoyle C_1—C_6, la soumission d'un composé de formule I où R_3 est —NH_2 à une alcoylation; ou

J: pour la préparation d'un composé de formule I où R_2, R_4 et R_5 sont tels que définis à la revendication 1 et R_3 est —CH_2NC, la soumission d'un composé où R_3 est un groupe



à une réaction avec PCl_3 en présence d'une amine;

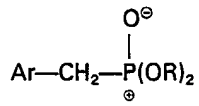
en ce qu'un composé ainsi obtenu de formule I, si on le souhaite, est réduit en dérivé 2,3-dihydro-5,6,7,8-tétrahydro- ou 2,3,5,6,7,8-hexahydro correspondant; et en ce qu'un composé obtenu selon l'un des procédés décrits ci-dessus, si on le souhaite, est transformé en un sel.

14. Procédé selon la revendication 13, caractérisé en ce que dans le procédé

A: Z'' représente un halogène, du tosyle ou du mésyle et la réaction est effectuée par chauffage des réactifs ensemble dans un solvant inerte;

B: quand Z représente un halogène, on utilise un catalyseur de cuivre;

C: le réactif de Wittig utilisé a pour formule



avec Ar étant tel que défini à la revendication 1, R étant un groupe hydrocarbure;

E: X représente un halogène, un alcoxy, un aryloxy, un mésyle, un tosyle, un groupe quaternaire, de préférence $\overset{\oplus}{N}(CH_3)_3I^{\ominus}$, ou un groupe quaternaire où l'ion quaternaire est un contre-ion non nucléophile choisi parmi $BF_4^{\ominus}$, $PF_6^{\ominus}$, $CF_3SO_3^{\ominus}$, et $FSO_3^{\ominus}$ et le cyanure de métal est un cyanure d'un métal alcalin;

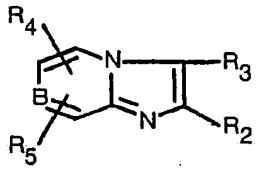
F: la réduction est effectuée au moyen d'hydrure de lithium aluminium;

G: la nitrosation est effectuée au moyen d'un nitrite, de préférence du nitrite de sodium, en présence de HCl concentré;

H: la réduction est effectuée au moyen de poudre de zinc dans l'acide acétique.

Revendications pour l'Etat contractant: AT

1. Procédé pour la préparation d'imidazo[1,2-a]pyridines et pyrazines de formule générale



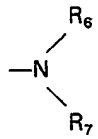
où B est CH ou N, et quand B est CH, alors

R_2 est hydrogène, alcoyle C_1—C_6 ou hydroxyalcoyle C_1—C_6;

R_5 est hydrogène, halogène ou alcoyle C_1—C_6;

et *soit*

R_3 est alcoyle C_1—C_6, —CH_2CN, hydroxyalcoyle C_1—C_6, —NO, —CH_2NC,



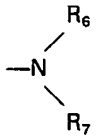
ou, à condition que R_2 ne soit pas de l'hydrogène, également de l'hydrogène et

R_4, étant attaché à toute position 5-, 6- ou 7- du noyau, représente l'un des groupements —O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar, —CH=CH—CH_2—Ar ou —O—CH_2—CH=CH_2; ou

R_3 est tel que défini ci-dessus et

R_4, étant attaché à la position 8 du noyau, représente l'un des groupements: —CH=CH—Ar, —CH=CH—CH_2—Ar ou —O—CH_2—CH=CH_2; ou

R_3 est —NO, —CH_2NC ou



et

R_4, étant attaché à la position 8 du noyau, représente —O—R_8—Ar, —NH—R_8—Ar ou —R_8—Ar;

et quand B est N, alors

R_5 est tel que défini ci-dessus,

R_2 et R_3 sont indépendamment choisis parmi l'hydrogène, un alcoyle C_1—C_6, un hydroxyalcoyle C_1—C_6, —CH_2CN, —NO et —NR_6R_7 et

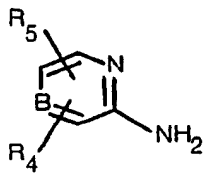
R_4 est —O—R_8—Ar, —NH—R_8—Ar, —R_8—Ar, —CH=CH—Ar ou —CH=CH—CH_2—Ar;

et dans les définitions ci-dessus, R_6 et R_7 sont indépendamment choisis parmi l'hydrogène ou un alcoyle C_1—C_6;

R_8 est un groupe alcoylène C_1—C_6 à chaîne droite ou ramifiée et

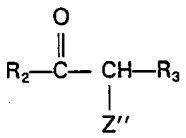
Ar représente thiényle, furanyle, pyridyle, phényle ou phényle substitué par un ou plusieurs substituants choisis parmi un halogène et un alcoyle C_1—C_6;
leurs dérivés 2,3-dihydro; 5,6,7,8-tétrahydro et 2,3,5,6,7,8-hexahydro et les sels acceptables en pharmacie de tels composés; caractérisé en ce que

A: on fait réagir un composé de formule générale



II

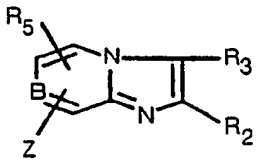
avec un composé de formule générale



III

et dans les formules, R_2, R_3, R_4 et R_5 sont tels que définis à la revendication 1, à l'exception que tout groupe amino ou hydroxy libre présent dans R_2 ou R_3 peut être protégé par un groupe protecteur qui est subséquemment retiré et Z'' représente un bon groupe partant; ou

B: pour la préparation de composés où R_4 est —O—R_8—Ar, —O—CH_2—CH=CH_2, —NH—R_8—Ar, —R_8—Ar, avec R_8 et Ar étant tels que définis à la revendication 1, on fait réagir un composé de formule générale



IV

avec un composé de formule générale

Hal—Z'

et dans les formules ci-dessus, R_2, R_3 et R_5 sont tels que définis à la revendication 1, Hal représente Br, Cl ou I,

Z représente un halogène, OH ou NH_2 et

Z' représente —R_8—Ar ou CH_2—CH=CH_2.

C: pour la préparation de composés où R_4 représente —CH=CH—Ar ou —CH=CH—CH_2—Ar, un composé de formule IV où R_2, R_3 et R_5 sont tels que définis à la revendication 1 et Z représente CHO est soumis à une réaction de Wittig avec le réactif approprié de Wittig; ou

D: pour la préparation de composés de formule I où R_4 représente —CH=CH—Ar, la réaction d'un composé de formule IV où R_2, R_3 et R_5 sont tels que définis à la revendication 1 et Z représente un groupe phosphinylméthyle, avec un composé de formule Ar-CHO par lequel Ar est tel que défini ci-dessus; ou

E: pour la préparation d'un composé de formule I où R_2, R_5 et R_5 sont tels que définis à la revendication 1 et R_3 représente CH_2CN, la réaction d'un composé de formule I où R_3 est un groupe —CH_2X, X étant un bon groupe partant, avec un cyanure de métal; ou

F: pour la préparation de composés de formule I où R_2, R_3, R_4 et R_5 sont tels que définis à la revendication 1, à l'exception qu'au moins l'un de R_2 et R_3 doit être un hydroxyalcoyle inferieur, la réduction d'un composé de formule I où R_2 et/ou R_3 est un groupe —$(R')_nCOOR$, R' étant un groupe alcoylène inferieur ayant 1 à 5 atomes de carbone, n étant zéro ou un et R étant un groupe hydrocarbure; ou

G: pour la préparation de composés de formule I où R_2, R_4 et R_5 sont tels que définis à la revendication 1, et R_3 est —NO, la soumission d'un composé de formule I où R_3 est de l'hydrogène à une nitrosation, à la position 3, ou

H: pour la préparation de composés de formule I où R_3 est —NH_2 et R_2, R_4 et R_5 sont tels que définis à la revendication 1, la réduction d'un composé de formule I où R_3 est —NO ou NO_2; ou

I: pour la préparation de composés de formule I où R_2, R_4 et R_5 sont tels que définis à la revendication 1 et R_3 est —NR_6R_7 avec R_6 et/ou R_7 étant un alcoyle inferieur, la soumission d'un composé de formule I où R_3 est —NH_2 à une alcoylation; ou

J: pour la préparation d'un composé de formule I où R_2, R_4 et R_5 sont tels que définis à la revendication 1 et R_3 est $—CH_2NC$, la soumission d'un composé où R_3 est un groupe

$$—CH_2NHCH \overset{\|}{O}$$

à une réaction avec PCl_3 en présence d'une amine;
en ce qu'un composé ainsi obtenu de formule I, si on le souhaite, est réduit en dérivé 2,3-dihydro-, 4,5,6,7,8-tétrahydro- ou 2,3,5,6,7,8-hexahydro correspondant; et en ce qu'un composé obtenu selon l'un des procédés décrits ci-dessus, si on le souhaite, est transformé en un sel.

2. Procédé selon la revendication 1, caractérisé en ce que dans le procédé

A: Z'' représente un halogène, du tosyle ou du mésyle et la réaction est effectuée par chauffage des réactifs ensemble dans un solvant inerte;

B: quand Z représente un halogène, on utilise un catalyseur de cuivre;

C: le réactif de Wittig utilisé a pour formule

$$Ar—CH_2—\overset{\oplus}{P}(OR)_2 \quad (O^{\ominus})$$

avec Ar étant tel que défini à la revendication 1, R étant un groupe hydrocarbure;

E: X représente un halogène, un alcoxy, un aryloxy, un mésyle, un tosyle, un groupe quaternaire, de préférence $\overset{\oplus}{N}(CH_3)_3I^{\ominus}$, ou un groupe quaternaire où l'ion quaternaire est un contre-ion non nucléophile choisi parmi $BF_4^{\ominus}$, $PF_6^{\ominus}$, $CF_3SO_3^{\ominus}$, et $FSO_3^{\ominus}$ et le cyanure de métal est un cyanure d'un métal alcalin;

F: la réduction est effectuée au moyen d'hydrure de lithium aluminium;

G: la nitrosation est effectuée au moyen d'un nitrite, de préférence du nitrite de sodium en présence de HCl concentré;

H: la réduction est effectuée au moyen de poudre de zinc dans l'acide acétique.

3. Procédé selon la revendication 1 ou 2, caractérisé en ce que les composés de formule I où B est CH, R_2 représente $—CH_3$ ou $—CH_2CH_3$;

R_5 représente de l'hydrogène ou $—CH_3$;

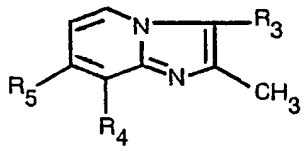
R_3 représente $—NH_2$, $—NHC_2H_5$, $—CH_2CN$ ou $—CH_3$ et

R_4, étant attaché à la position 5-, 6- ou 7- du noyau, représente $—O—R_8—Ar$, $—NH—R_8—Ar$, $—R_8—Ar$, $—CH=CH—Ar$ ou $—CH=CH—CH_2—Ar$, avec R_8 étant méthylène, éthylène ou propylène et Ar étant phényle, o-fluorophényle, p-fluorophényle, p-chlorophényle, thiényle ou furanyle, sont préparés.

4. Procédé selon la revendication 1 ou 2, caractérisé en ce que les composés de formule I où B, R_2 et R_5 sont tels que définis à la revendication 3; R_4 étant attaché à la position 8 du noyau, est tel que défini à la revendication 3 et R_3 représente $—NH_2$ ou $—NHC_2H_5$, sont préparés.

5. Procédé selon la revendication 1 ou 2, caractérisé en ce que les composés de formule I où B, R_2 et R_5 sont tels que définis à la revendication 3, R_3 est $—CHCN$ ou $—CH_3$ et R_4, étant attaché à la position 8 du noyau, est $—CH=CH—Ar$ ou $—CH=CH—CH_2—Ar$, avec Ar étant tel que défini à la revendication 3, sont préparés.

6. Procédé selon la revendication 1 ou 2, caractérisé en ce que les composés de formule



IA

où

R_3 est $—NH_2$;

R_4 est $—CH_2—CH_2—Ar$ ou $—CH_2—CH_2—CH_2—Ar$ et

R_5 est hydrogène ou méthyle, et

Ar est phényle ou thiényle, sont préparés.

7. Procédé selon la revendication 1 ou 2, caractérise en ce que les composés de formule IA indiqués à la revendication 6, où

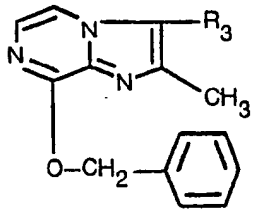
R_3 est $—NH_2$, $—CH_2CN$ ou $—CH_3$

R_4 est $—CH=CH—Ar$ ou $—CH=CH—CH_2—Ar$ et

R_5 est hydrogène ou méthyle, et

Ar est phényle ou 3-thiényle, sont préparés.

8. Procédé selon la revendication 1 ou 2, caractérisé en ce que les composés de formule



où

R_3 est alcoyle C_1—C_6, —CH_2CN, —NH_2, ou —NHC_2H_5, sont préparés.

9. Procédé selon la revendication 1 ou 2, caractérisé en ce que les composés 3 - amino - 2 - méthyl - 8 - (2 - phényléthyl) - imidazo[1,2 - a]pyridine; 2,3 - diméthyl - 8 - (2 - phényl - éthényl) - imidazo[1,2 - a]pyridine et 3 - cyanométhyl - 2 - méthyl - 8 - [E - 1 - (3 - phényl - propén - 1 -yl)] - imidazo[1,2 - a]pyridine, sont préparés.

10. Procédé selon la revendication 1 ou 2, caractérisé en ce que les composés 8 - benzyloxy - 3 - cyanométhyl - 2 - méthyl - imidazo[1,2 - a]pyrazine; 8 - benzyloxy - 2,3 - diméthyl - imidazo[1,2 - a]-pyrazine et 3 - amino - 8 - benzyloxy - 2 - méthyl - imidazo[1,2 - a]pyrazine sont préparés.